Demonstration of a tool to assess cumulative risks from combined exposure to multiple pesticide residues in fruits and vegetables

Project Kennis- en modelkoppelingen voor borging voedselveiligheid in de groenten- en fruitsector

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Summary

This report presents the IPGF tool for performing risk calculations based on the pesticide residues monitoring data collected by the Dutch private vegetable and fruit sector organised in the Foundation Food Compass. The IPGF tool is an online platform, where IPGF is the acronym of *Impactanalyse Pesticiden in Groenten en Fruit* (*impact analysis of pesticides in fruit and vegetables*). The tool is developed to allow the Dutch private sector to perform cumulative risk calculations for pesticides in fruit and vegetables using a secure web service connection with the publicly developed Monte Carlo Risk Assessment (MCRA) web platform that is available at the Dutch national institute for public health and the environment (RIVM) and is the selected platform of the European Food Safety Authority (EFSA) for pesticide cumulative risk assessments. In addition to the cumulative risk calculations, the IPGF tool can also evaluate per-substance indicators based on legal requirements regarding the maximum residue limits (MRL) and acute reference doses (ARfDs), and it can evaluate compliance with private retail requirements of Dutch retailers. The potential of the IPGF tool is demonstrated in an artificial case study in which the Food Compass monitoring data of the years 2013-2021 were analysed. For each year in this period, the various occurrence, exposure and risk indicators were evaluated. Also a comparative analysis was done over all the years to obtain insights in possible trends. The results provide insight in the steps towards future use of the tool by the Dutch private sector as part of the food safety monitoring program. The report concludes with suggestions for further implementation.

1 Introduction

In the public-private partnership project *Kennis- en modelkoppelingen voedselveiligheid* (KMKVV), a tool was created for assessing the cumulative human health risk of intake of pesticide residues in fruits and vegetables based on the monitoring data of the Dutch private companies, organised in Stichting Food Compass. This tool, named IPGF, is an online platform where IPGF is the acronym of *Impactanalyse Pesticiden in Groenten en Fruit* (*impact analysis of pesticides in vegetables and fruit*) and it uses a web service connection with the publicly developed Monte Carlo Risk Assessment (MCRA) web platform for performing the cumulative risk assessment calculations. The tool can be used to perform both cumulative risk calculations and the traditional by-substance analyses on batches of samples (e.g. per year). The tool also allows to evaluate samples for compliance with private retail requirements of Dutch retailers.

The rationale for developing the IPGF tool is that the presence of multiple pesticide residues on fruits and vegetables causes potential health risks for consumers. At present, the sector does not have access to the advanced models for performing cumulative risk calculations. According to the General Food Law (Regulation (EC)178/2002), food business operators are responsible for ensuring food safety of the food products placed in the market. Food Compass is a foundation in which food business operators can participate to take part in sectoral residue monitoring program to monitor the potential health risks from intake of pesticide residues. Currently, pesticide residue levels on food products are evaluated per sample and substance by substance by comparing the concentration levels with the maximum residue limits (MRLs) and IESTI (International Estimate of Short-Term Intake) intake estimates with the acute reference doses (ARfDs). However, there is also a growing concern about the combined effects of the intake of multiple pesticides, which is not addressed by these substance-by-substance evaluations. This concern has led to additional non-statutory restrictions by retailers, such as a maximum limit on the number of active substances allowed to be present simultaneously on one product.

Regulation (EC) No. 396/2005 states that cumulative and synergistic effects of pesticides should be taken into account for dietary risk assessment when appropriate methodologies are available. Over the last decade these methods were developed by EFSA, RIVM and WUR, and have been implemented in the Monte Carlo Risk Assessment (MCRA) web platform. However, grouping of pesticides in cumulative assessment groups, i.e. groups of pesticides that can lead to the same health effect, is still ongoing at EFSA, and groups have as yet only been defined for some forms of craniofacial alterations as a developmental effect, some neurological effects and some thyroid effects (EFSA 2013, EFSA 2019c, EFSA 2019d, EFSA 2021). Whilst implementation and further development at the regulatory level is still ongoing, these methods are in a state that technically allows them to be used on the pesticide monitoring data of Food Compass. Having access to these publicly developed methods allows the fruits and vegetables sector to evaluate cumulative effects of exposure to multiple pesticides for monitoring the risks in a science-based approach. Figure 1 illustrates the role of the IPGF tool in the public/private landscape for safeguarding against cumulative effects of combined exposure to pesticide residues in fruits and vegetables.

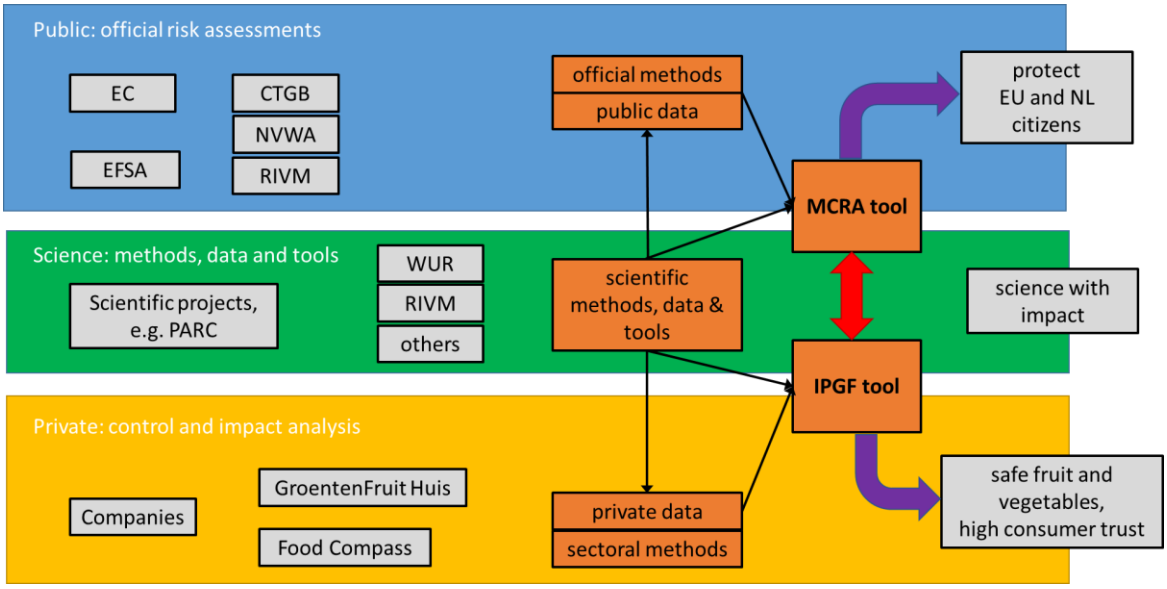

Figure 1 Public and private landscape for safeguarding against cumulative effects of combined exposure to pesticide residues.

For demonstrating the IPGF portal, this report presents the results of a practical case study in which risk calculations were performed on the Food Compass monitoring data 2013-2021, expanding on the preliminary version of this work (van der Voet et al. 2021). The calculations are not compliant with EU regulatory risk assessments as would be performed by for example RIVM or EFSA. This is due to some intended deviations from the regulatory accepted methodology and insufficient availability of certain data. In particular, in order to demonstrate the technical functionality of the methods, the IPGF tool was applied to a larger collection of cumulative assessment groups (CAGs), derived by Nielsen et al. (2012), that are not endorsed by EU, EFSA or RIVM. In addition, the grouping is done at organ level and not at the level of specific phenomenological effect and the calculations use acute reference doses as toxicological reference values instead of references values derived for the specific organ level effect. These choices make the calculations very conservative. Consequently, the results presented in this report should not be interpreted as results of risk assessments compliant with EU accepted methods, but as a demonstration of the IPGF tool and of how the functionality of MCRA to perform cumulative risk calculations can be made available to the private sector for monitoring the safety of its products.

For each batch consisting of the samples collected during a year, the analysis included traditional by-substance analyses, cumulative risk analyses and analyses of violations of retail requirements. The main indicator of the case study is the hazard index (HI) measuring the risk to the Dutch population of cumulative exposure due to the combined intake of multiple pesticide residues in their diet, to compare these results to other existing approaches and to evaluate the trends over time. If potential concerns were observed, it was of interest to know which pesticides, foods, and combinations of pesticide and food contributed most.

An additional aim of the study was to compare signalling of potential risk drivers as currently performed by Food Compass to a potential signalling system using the cumulative risk assessment results. The current system inspects results for single food samples and relies on finding MRL (maximum residue level) and ARfD (acute reference dose) exceedances for single substances, and detection of residues of specific classes of chemicals, such as carcinogenic, mutagenic or reprotoxic (CMR) substances. To allow such a comparison these methods were also included in the IPGF tool.

Another additional aim was to study the signalling of potential problems based on private retail criteria applied by various retail organisations. To allow such a

comparison, retail criteria analysis functionality has also been implemented in the IPGF tool.

Any (cumulative) risk assessment has uncertainties due to limited knowledge about working mechanisms and limited availability of data. Whereas such uncertainties have been extensively overviewed by EFSA in recent cumulative risk assessment reports, we address these uncertainties shortly in the report, with special emphasis on issues that are specific in our demonstration.

2 Data

2.1 Food products

The food products of interest are all fruits and vegetables falling under the remit of the monitoring program of Food Compass. In line with the EU regulatory accepted methods for cumulative exposure assessments, also drinking water is included in the assessment as a potential source of exposure using the same assumptions as in the Tier II calculations of van Klaveren et al. (2019a) and EFSA (2020a).

In the monitoring data of Food Compass, the food products are coded using a coding system derived from the EC food code description laid down in Annex I to Regulation (EC) No 396/2005[1]. In the modified coding scheme adopted by Food Compass, the first digit is removed (because this digit is always zero for fruits and vegetables) and two digits are added at the end of the food codes to indicate further specification of sub-products. E.g., the EC food code for grapefruits is 0110010, which has the FC food code 11001001. Shaddocks and pomelos, falling under the EC food code of grapefruits have the product codes 11001002 and 11001003 respectively (see example in Table 1).

For the calculations of the present case study, the foods catalogue of Food Compass was retrieved in October 2022. The catalogue contains 493 foods in total of which 222 at main group level and 271 at sub-product level.

The consumption data and other data for cumulative exposure assessment was coded using EFSA MATRIX codes (EFSA, 2020c), which is also based on the EC food codes. The mapping between the Food Compass food codes and the EFSA MATRIX codes was done automatically. For the food products monitored by Food Compass, the corresponding MATRIX code is obtained by prefixing the EC food code with a 'P' and adding a 'A' at the end. E.g., for grapefruits the corresponding MATRIX code is P0110010A.

Table 1 Example of the food coding of grapefruit and related varieties in the Food Compass coding system, the EC coding system and the EFSA MATRIX coding system.

FC Food Code	FC Food Name	Is main level	EC Food Code	EC Food Name	EFSA MATRIX Code
11001001	Grapefruits	Yes	0110010	Grapefruit	P0110010A
11001002	Shaddock	No	0110010	Shaddocks	
11001003	Pomelo	No	0110010	Pomelos	
11001004	Sweetie	No	0110010	Sweeties	
11001005	Tangelo	No	0110010	Tangelo (except mineola)	
11001006	Ugli	No	0110010	Ugli and other hybrids	

The cumulative exposure assessments are performed at the level of the EFSA MATRIX codes, and all Food Compass sub-product samples are grouped at this main product level. I.e., samples for grapefruits, shaddocks and pomelos are all combined under the main food product grapefruits.

[1] http://data.europa.eu/eli/reg/2018/62/oj

2.2 Substances

The complete substances catalogue of Food Compass as considered in the calculations contains 1457 substance definitions (retrieved in October 2022). This comprises all substances measured in the monitoring program of Food Compass and the active substances associated with these measured substances (e.g., complex residue definitions / sum-substances). In this study, all active substances that are classified as a CMR substance (carcinogenic, mutagenic, reprotoxic), a substance of which the genotoxic potential cannot be ruled out (e.g., chlorpyrifos and dimethoate), or that are associated with one or more acute adverse health effects are considered in the impact assessments.

Table 2. Substances catalogue of Food Compass

Total	1457
CMR	16
Substances of which the genotoxic potential cannot be ruled out	17
Active substances associated with acute adverse health effect	448

The substance coding system adopted by Food Compass is based on CAS-numbers, but complemented with additional substance codes for (complex) residue definitions/sum-substances that do not have a CAS code. Where possible, a mapping was made between this CAS-based coding system and the EFSA PARAM coding system, needed to align some EFSA datasets (e.g., the EFSA processing factors database). This mapping was possible for 855 of the 1457 substances.

2.3 Monitoring data (Food Compass)

Monitoring data for the years 2013-2021 were obtained from the Food Compass database via the web service retrieved on 25-27 October 2022. For each year, the samples were combined in a batch for which the risk calculations of that year were performed.

The Food Compass monitoring programme consists of approximately 1.500 samples that are taken on fresh unprocessed fruits and vegetables. The sampling scheme is based on a risk assessment that includes data on MRL exceedances and trade data of almost 200 different products. Besides the Food Compass samples also data from NVWA and several companies (originating from their own sampling programme) are included in the database (up to 2017). Starting in 2021, again the sampling data of some 20 companies are included in the database, which more than doubles the total number of samples.

For each sample, the Food Compass web service reports the measured food, the laboratory that performed the analysis, the analysis method that was used, and the positive concentrations (i.e., the measurements above limit of reporting). Cumulative analyses also require information on the analysed substances for which the measurements were below the limit or detection / reporting. This information was obtained from the laboratory scope lists. These lists provide, for each laboratory, the information of the measured substances and the reporting limits for each analysis method in a given time frame. The analytical scopes and their related substance reporting limits were extracted from the analytical scope documents of the laboratories.

Table 3 summarizes the sizes of the sample batches and the number of food products analysed. Furthermore, the table reports the number of distinct foods from which the

samples were taken and counts of irregularities that were encountered when linking the sample reports to the known analytical laboratory scopes. These issues were classified in three categories; 1) invalid analytical scopes are reported analysis methods that did not match any known analytical method, 2) invalid measurements are reported substance concentrations for which the substance was not known to be part of the reported analytical method, and 3) the non-critical measurement inconsistencies were, e.g., double reports of the same substance, both as active substance and as part of the sum-substance or residue definition.

Table 3 Food samples of the batches imported from Food Compass.

Year	Total samples	Number of sampled food products	Samples[1] with invalid analytical scopes	Samples[1] with invalid measurements	Samples with non-critical measurement inconsistencies	Samples available for cumulative analyses
2013	4376	114	92	361	458	4376
2014	3771	101	4	324	504	3767
2015	3732	104	28	429	538	3732
2016	3244	105	0	303	473	3244
2017	3372	99	0	332	447	3372
2018	2165	93	0	176	438	2165
2019	1710	99	1	171	351	1710
2020	1472	95	2	144	333	1472
2021	2370	96	1	138	740	2370

[1] These samples may still contain valid data for other analysis methods/substances.

2.4 Health effects and cumulative assessment groups

Cumulative exposure and risk calculations are performed for groups of chemicals associated with a common adverse health effect. This grouping is done at different levels; 1) grouping of chemicals affecting the same target organ, 2) grouping based on a common specific phenomenological effect, 3) grouping based on a common mode of action, 4) grouping of chemicals based on a common mechanism of action (EFSA, 2014). Grouping at the (lower) organ level leads to larger groups of chemicals, but may also include combinations of chemicals for which there is no combined cumulative effect. At higher levels, the groups will become more fine-grained, leading to more, yet smaller groups of chemicals. Establishment of these groups is a complex and time-consuming process, in which the complexity increases with the level of grouping. There is a trade-off between using the easier to establish but more conservative lower-level groupings versus the more realistic, but also more time-consuming to establish, higher level groupings.

Although the development of the cumulative assessment groups is still in progress at EFSA/EC level, grouping substances based on a common specific phenomenological effect (i.e., level 2) has been chosen as the European standard for cumulative risk assessment and EFSA has published a guidance on how to establish the groups of chemicals that should be included in a common assessment (EFSA, 2021b). At present, EFSA has published cumulative assessment groups (CAGs) of pesticides with acute effects on the nervous system (EFSA, 2019c.) and CAGs of pesticides with chronic effects on the thyroid system (EFSA, 2019d.).

It should be noted that for EU regulatory accepted risk assessment, the CAGs developed by EFSA should be used. However, for demonstrating the IPGF tool a different collection of CAGs was used, derived by Nielsen et al. (2012). This collection of CAGs is not endorsed by EU, EFSA or RIVM for risk assessment. It was selected, however, because it contained groupings for a large number of organs, allowing to test and demonstrate the tool on multiple groups. In addition, for this demonstration, grouping was done at the level of target organ (i.e., level 1, see Table 4). As mentioned, these groups can be considered to yield more conservative cumulative risk estimates, but have more coverage in terms of the possible adverse health effects considered in the assessment. In this study, only acute effects were considered.

Table 4 Organ level assessment groups for acute cumulative exposure assessment.

CAG	Organ	Number of active substances
CAG-01	Adrenal gland	10
CAG-02	Bone marrow	9
CAG-03	Cardiovascular system	10
CAG-04	Developmental/reproductive system	110
CAG-05	Eye	39
CAG-06	Haematological system	68
CAG-07	Kidney	47
CAG-08	Liver	100
CAG-09	Muscle	10
CAG-10	Nervous system	54
CAG-11	Parathyroid system	5
CAG-12	Skeleton	3
CAG-13	Spleen	9
CAG-14	Thyroid	32
CAG-15	Urinary bladder	14

It is important to note that the assessment groups may contain pesticides that are not authorised, for example because they belong to the category of carcinogenic, mutagenic, or toxic for reproduction (CMR) substances. These substances have no ARfDs and therefore it is also not possible to derive relative potency factors from such values. Such substances essentially need to be controlled at the single-substance level. Nevertheless, it would be wrong to ignore these substances, when found, in cumulative risk assessments. Consequently, non-authorised substances were included in the cumulative assessments by using best estimates of hazard characterisation, either from historical ARfD values, or from specific dossiers from EFSA.

2.5 Hazard characterisations

For the cumulative risk calculations, a hazard characterisations database was created from the ARfD database of GroentenFruit Huis retrieved on 20-04-2022. This database was modified to also include reference doses for substances associated with acute health effects without an effective ARfD. This can occur when substances are not or no longer authorised, for instance because they are CMR. For the cumulative health impact assessments, these substances should also be included and therefore require a

reference value that is associated with the health effect of the CAG. For these substances, the last effective ARfD or a suggested suitable reference value from dossiers from EFSA were used to characterise the hazard.

The ARfDs used for the IESTI calculations were obtained in real time from the GroentenFruit Huis web portal during the calculations.

2.6 Maximum residue levels

MRLs are only used for the deterministic calculations, for evaluating whether the positive concentrations exceed the legal limits. For each positive substance concentration, the limit value used for this calculation was the limit value that was applicable at the time of sampling. A database with MRL values for substance/food combinations is maintained at the GroentenFruit Huis web portal which is regularly updated based on new legislation using the information published on EU Pesticides database[2]. For each sample, the MRL applicable at the time of sampling was used. The MRLs used for the MRL exceedance calculations were retrieved on November 2022 from the GroentenFruit Huis web portal and contained all MRLs over the period of the trend-analysis (2013-2021).

2.7 Private retail requirements

Retail restriction rules of six retailers active on the Dutch market were considered for analysing the compliance of the samples with these retail requirements. The retail restrictions are composed of five types of rules, evaluated for each sample, for which each retailer adopts different thresholds. These are:

- Maximum threshold for the highest %MRL of substances measured on the sample.
- Maximum threshold for the sum of the %MRL values of all substances measured on the sample.
- Maximum threshold for the highest %ARfD of substances measured on the sample.
- Maximum threshold for the sum of the %ARfD values of all substances measured on the sample.
- Maximum threshold for the total number of active substances in the sample, or any substances that appear on the retailer's blacklist.

The specific thresholds for these rules set by the retailers at the time of the trendanalysis are shown in Table 5. Note that due to missing information about the substances on the retailers' blacklists, for the last rule only the maximum number of active substances was evaluated.

Table 5. Retail requirements set by the retailers at the time of the trendanalysis.

Retailer	Max %MRL active substance	Max sum %MRL/sample	Max %ARfD active substance	Max sum %ARfD/sample	Max nr. of active substances/sample
Retailer I	33.3	80	80	80	3
Retailer II	70	80	100		5
Retailer III	50				
Retailer IV	50		50		
Retailer V	50				
Retailer VI	50		50		

[2] https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/start/screen/mrls/download

2.8 Consumption data

For the IESTI calculations, the large portion consumer amounts consumption data of the critical population are obtained from the GroentenFruit Huis web portal which are based on EFSA's PRIMo v3.1 model (EFSA, 2019b).

For the cumulative exposure calculations, consumption data from the Dutch food survey (VCP) for the child population (2-6yr) 2005-2006 was used. The data has been provided by RIVM to EFSA and has been provided again by EFSA in the form of raw primary commodity (RPC) consumption data (EFSA 2019a), meaning that the consumptions are expressed in terms of the raw (measured) food products.

2.9 Processing factors and reverse yield factors

For the deterministic calculations, the processing factors of EFSA's PRIMo v3.1 model were used in combination with a processing factors database of RIVM[3], obtained from the database maintained at GroentenFruit Huis.

For the probabilistic calculations, a different (yet partly overlapping) dataset of processing factors was used. This database of processing factors was obtained from the EFSA database of processing factors prepared by Scholtz et al. (2018). Since this dataset reports the substances using PARAM codes, a mapping between PARAM codes and the CAS-based codes of Food Compass was used to make this database suitable for the calculations. For observed risk driving combinations of food and substance, this processing factors dataset was further extended with additional processing factors from the RIVM database and extrapolated processing factors. The reverse yield factors, being the factors that describe the weight reduction due to processing, were obtained from the raw primary commodity consumption data (EFSA 2019a).

2.10 Unit variability factors

For the deterministic calculations, the unit variability factors from EFSA's PRIMo v3.1 model were used, obtained from the database maintained at GroentenFruit Huis. For the probabilistic calculations, the same unit variability factors as used in the Tier II calculations of van Klaveren et al. (2019a) and EFSA (2020a) were used. Note that these studies focused on a subset of 30 raw food products, therefore only unit variability factors for these food products are available.

2.11 Substance translations

For the probabilistic calculations, exposures are calculated at the level of active substances. However, many substance residues are reported at the level of (complex) residue definitions and require translation to the associated active substance(s). For this, substance translation definitions are used. The substance translations used in this case study are extracted from the substances hierarchy. Due to insufficient availability of detailed information, the translations were constructed with a default scheme such that in the active substance allocation process, each measured substance is (randomly) allocated to one of the active substances with equal probabilities and a conversion factor of one.

[3] https://www.rivm.nl/en/chemkap/fruit-and-vegetables/processing-factors

3 Method

Three different categories of indicators were considered in this case study: hazard index statistics and percentages contribution from cumulative impact analyses (Section 3.1), per-sample analyses based on legal requirements (Section 3.2), and analysis of the additional private restrictions adopted by retailers (Section 3.3).

In the probabilistic cumulative assessments, all samples collected during a year were analysed collectively on cumulative, i.e. multiple-substance, health impacts. This yields impact indicators that include both aggregated risk of intake of multiple foods and the cumulative exposure of multiple substances. Probabilistic results are referring to percentile points of distributions in the population of all individual-days, i.e. these distrutions aim to be representative for the population on any day in the year under analysis.

In contrast, deterministic results were produced by simple calculations, typically based on conservative input values. These indicators are computed per sample and therefore refer to just single food products. Aggregate summary statistics are computed when considering the set of samples in a year.

3.1 Probabilistic cumulative impact assessments

Probabilistic cumulative impact calculations were performed for each batch of samples collected during a year, over the years 2013-2021. The aim of the cumulative analyses was to assess the risk for the Dutch population population of acute cumulative adverse health effects caused by intake of pesticide residues via consumption of fruits and vegetables, assuming the residue levels of the products monitored by Food Compass in each year of the period 2013-2021. The targeted scope of the cumulative impact assessments is captured in more precise definitions in Table 6.

Table 6. Targeted scope definitions.

	Scope (targeted)
Chemicals	All pesticides applied in the production process that have a potential to leave residues on the scoped food products.
Routes and sources	The contribution to the risk via consumption of fruit and vegetables and drinking water. That is, we focus on the dietary route of exposure, and restrict the sources to all fruits and vegetables monitored by Food Compass and drinking water. Since there are other potential sources of exposure that may contribute to the health risk (e.g., chemical residues in animal products or non-dietary exposures from operators/bystanders in the fields), the risk calculations restricts to characterising the contribution of the considered route and sources of exposure to the total risk.
Health effects	Acute adverse health effects that may be caused by intake of the scoped chemicals.
Population	The Dutch population population in the present time frame.

For each acute health effect considered in this study (see Table 4), a cumulative risk calculation is performed. The cumulative risk calculations follow a probabilitisc modelling approach for the calculation of dietary exposures based on simulation of 100.000 simulated individuals obtained from random matching of individual day consumption data with occurrence data on the consumed products. The main result of the cumulative calculations is the hazard index (HI) at the p99.9 percentile of the distribution of the cumulative exposure of the individual days of the evaluated population. In addition to the overall impact for each health effect, also contributions of

the substances, foods, and combinations of food and substance to the overall risk are of interest.

Calculation of dietary exposures and risks is done in principle according to EC 2018 Tier 2 settings (see van Klaveren 2019a, EFSA 2020a). That is, simulated substance residues are generated using a sample-based approach, processing factors are used in the calculation, and unit-variability is accounted for in a beta model allowing simulated unit concentrations to be higher or lower than the composite value. Besides the use of different datasets (see Section 2), there are four aspects in which the calculations differ from the EC 2018 Tier 2 specification; calculation of occurrence frequencies (see Section 3.1.1), extrapolation of occurrence data (see Section 3.1.2), substance conversion (see Section 3.1.3), and characterisation of the hazard and risk (see Section 3.1.4).

Quantification of sampling uncertainty of consumption and occurrence data was done by re-running the Monte-Carlo simulation 100 times with bootstrapped consumption and occurrence datasets. For the overall HI, this quantified uncertainty was reported using the 95% confidence interval (lower and upper uncertainty limits p2.5 and p97.5 respectively).

3.1.1 Concentration modelling and occurrence frequencies

Concentration modelling is done according to the EC 2018 Tier 2 specifications, where the observed co-occurrences of substances in samples are preserved. Values reported to be below a certain limit (non-detects or non-reports) are replaced by 1/2 x LOR, where LOR is the limit of reporting, which can be either a limit of quantification (LOQ) or limit of detection (LOD) depending on the laboratory. Missing values, i.e. cases where measurements were missing for specific substances because they were not measured by the analytical method, are imputed using occurrence frequency estimates. Occurrence frequency estimates are estimates per combination of food and substance of the frequency/percentage that residues of the substance are present on the food (including residues with concentrations below the LOR). These frequencies are used for imputing censored and missing values with either a zero concentration or a positive concentration value. Occurrence patterns and frequencies are also computed the same way as in the EC 2018 Tier 2 method, except that no substance authorisation data to restrict use percentage upscaling to authorised uses was used, due to insufficient availability of data for this option.

3.1.2 Extrapolation of food samples

No extrapolation was done for food samples of foods with a limited amount of samples (data-poor foods) from other foods (data-rich foods) because extrapolation rules were not sufficiently available.

3.1.3 Substance conversion

Substance conversion rules are used to translate measured substance concentrations (e.g., of sum substances) to active substance concentrations. The substance translation rules were extracted from the sum-substance hierarchy information in the Food Compass substances catalogue. However, substance authorisations are not included in the substance conversion, since this information was not sufficiently available. By not including substance authorisations in the substance conversion step, substances can also be allocated to unauthorised active substances, even when the measured substance is also associated with an authorised active substance. Not including substance authorisations may result in more conservative exposure estimates.

Note that samples may have multiple sample analyses, measured using different analytical methods. It may occur that the same substance is measured by multiple analytical methods and that these methods report conflicting measurements for the same substance. This also occurs indirectly (via active substance allocation) when one analytical method reports the active substance concentration directly and another analytical method reports a sum-substance concentration that translates that active substance.

3.1.4 Characterisation of the hazard and risk

Whereas the risk metric prescribed by the EC 2018 Tier 2 methodology is the so called Total Margin of Exposure, in the present case study risks are summarized using the hazard index (HI) metric, which is the sum of the so-called hazard quotients (HQs) computed for all substances. The HQs are calculated by dividing the regulatory chosen 99.9th percentile of the exposure distribution by the ARfD of the substance. In this report, HQs and HIs are expressed as percentages.

The active substances of the assessment are obtained from data, which are further restricted to contain only the substances for which a reference value is available (see Section 2.5). The hazard characterisations are formed by ARfDs which apply to the critical effect that are used as a proxy for specific (organ / CAG level 1) effects in the cumulative exposure assessments. This is similar to the approach followed by te Biesebeek et al. (2021) where it was applied in the context of prioritisation to identify low-priority substances and priority organs. This is, however, different from the purpose for which it is applied in this case study. For each exposure assessment, the most toxic substance (i.e., the substance with the lowest ARfD) was selected as the reference substance.

3.1.5 Uncertainty analysis

All assessments contain biases and uncertainty. In the cumulative impact assessments presented in this report, uncertainty limits are derived using consumption and concentration data as primary uncertainty source only. Through the use of bootstrapping (a resampling approach) uncertainty distributions were simulated for the relevant statistics. However, there are also uncertainties not covered by the current analyses, emerging in different parts and different forms in the cumulative impact assessments. In this report we focus on the uncertainties in the cumulative probabilistic assessments. However, uncertainties are also involved in the deterministic (IESTI) exposure calculations. In those calculations, more conservative biases are expected than in the probabilistic assessments.

The cumulative exposure and risk assessments of (EFSA, 2020a, EFSA, 2020b, EFSA, 2021) included extensive analyses of unquantified uncertainty following the guidance on uncertainty analysis (EFSA, 2018). In the present case study, we restrict to identification of the uncertainty sources and a motivated estimate of the potential bias of the results.

3.2 Deterministic sample analyses based on legal requirements

The sample indicators based on legal requirements are detection residues of specific classes of substances, such as CMR substances, calculation of MRL exceedance, and IESTI calculations expressed as %ARfD.

3.2.1 Residue findings of CMR substances and/or substances of which the genotoxic potential cannot be ruled out

All samples are evaluated for positive residue findings of CMR and/or substances of which the genotoxic potential cannot be ruled out. These findings are summarized per sample in terms of a simple yes/no for findings of both classes of substances. These indicators are summarized over multiple samples in terms of counts/percentages over all samples of the batch, for each food, for each substance, and for each combination of food and substance.

3.2.2 MRL exceedance

Each positive substance residue of each sample is evaluated for exceedance of the MRL applicable at the time of sampling for that substance and the sampled food product by computing the percentage of the substance concentration compared to the MRL (%MRL). Substance concentrations are considered to exceed the MRL when this percentage is higher than 100%. For each sample, this yields a number of %MRL values for all detected substances for which an MRL is available. For each sample, %MRL results are summarized in terms of the maximum %MRL and the sum of the %MRL values of all substances.

The MRL results are summarized over all samples in a year as counts/percentages of MRL exceedance of all samples of a batch, for each food, for each substance, and for each combination of food and substance.

3.2.3 IESTI calculations and ARfD exceedance

EFSA's PRIMo rev 3.1 model (EFSA, 2018, EFSA, 2019b) was adopted for calculating the deterministic exposure estimates, which follows the IESTI methodology for obtaining acute exposure estimates. The exposure estimates are reported as a percentage of the acute reference dose (%ARfD, see Section 0). Every exposure estimate greater than the ARfD (i.e., IESTI > ARfD or %ARfD > 100) is reported as an ARfD exceedance. Calculation of the IESTI is done for each positive substance concentration of each sample for which an ARfD is available. For substances without an ARfD, e.g., unauthorised substances, no IESTI estimates are calculated. For each sample, it is reported whether the ARfD is exceeded for any substance and the highest %ARfD of and the sum of the %ARfDs over all substances is computed, which is a metric considered by the retail requirements.

For each batch of multiple samples of a year the total number and percentage of samples with an ARfD exceedance are reported over all samples of the batch, for each food, for each substance, and for each combination of food and substance.

3.3 Assessment of compliance with private retail requirements

Each sample is tested against each rule of each retailer (Table 5) in order to evaluate compliance. Results are summarised for each rule, assessing if it was violated for any of the retailers.

For batches of multiple samples, the counts/percentages of violations of each rule are over all samples of the batch, for each food, for each substance, and for each combination of food and substance. Also the counts/percentages of violations of any rule of any retailer are summarized.

4 Software: IPGF Portal

The IPGF portal is developed for performing the risk calculations on the concentration data of the database maintained by Food Compass as demonstrated in this report. It allows the users to calculate the cumulative risks for samples and batches of samples, to assess compliance with legal requirements using traditional deterministic indicators and to assess compliance with above legal retail requirements. In addition, it allows the user to compare the results of the analyses of multiple batches, for instance, of a year which is demonstrated in this report.

4.1 Web portal interface

Figure 2 shows a screenshot of the landing page of the IPGF portal for a logged-in user. Using the top navigation bar the user can navigate to one of the analysis pages, inspect the different that are data locally collected in the portal for use in the different analyses, administrators can perform some basic administration tasks (e.g., user management), and some basic help pages are provided.

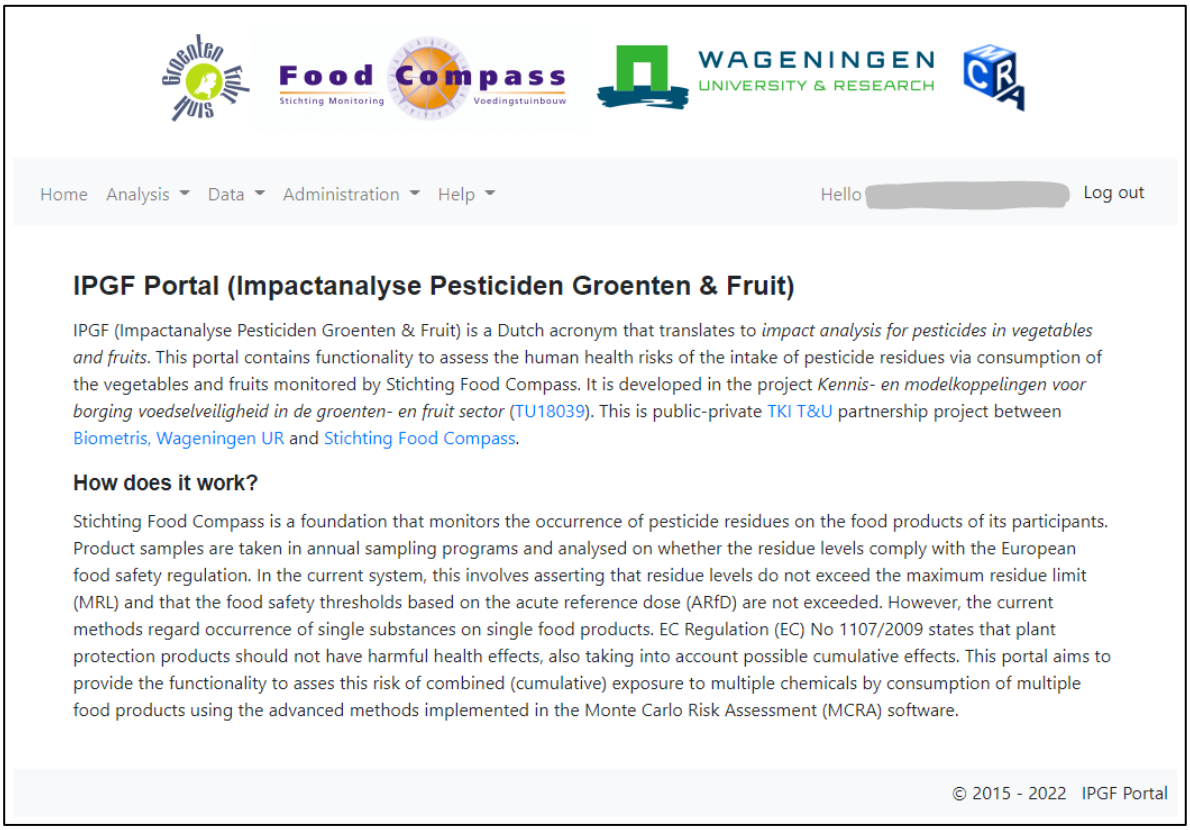

Figure 2 Screenshot of the IPGF portal home page for logged-in users.

There are three types of analysis offered by the portal:

- **Single sample analysis:** evaluate the substance residue levels of a single food sample. This sample can be one of the samples of the FoodCompass concentration database, or it can be an artificial sample created by the user.
- **Batch analysis:** evaluate the substance residue levels of a batch of multiple samples.
- **Batch comparison analysis:** combined comparative analysis of the results of multiple batch analyses, e.g., for the purpose of multi-year trend analysis.

4.1.1 Single sample analysis

For this sample, the analysis computes the deterministic indicators based on legal requirements and also compliance with the above legal retail restrictions. In addition, the single sample analysis offers the possibility to run cumulative exposure and risk calculations for this single sample. These are provided in two forms: 1) cumulative risk calculations with only this sample as occurrence data, and 2) cumulative risk calculations with occurrence data composed of the provided sample for the sampled food and use of a background sample collection for other foods. This way, the user is able to assess to potential health risks for the sampled food only and also to evaluate the health risk when other foods are included as well.

Figure 3 shows a screenshot of the single sample analysis page showing the results overview of a single sample analysis. The single sample analysis page has three tabs, one for specifying the samples, one for specifying the specific analysis settings, and when the results have been computed, the results of the analysis. The analysis results page is again split up into different sections; one being the overview section, then a page showing the results of the analysis for compliance with retail restrictions, the %MRL calculations, the deterministic %ARfD calculations, and the results of the probabilistic calculations.

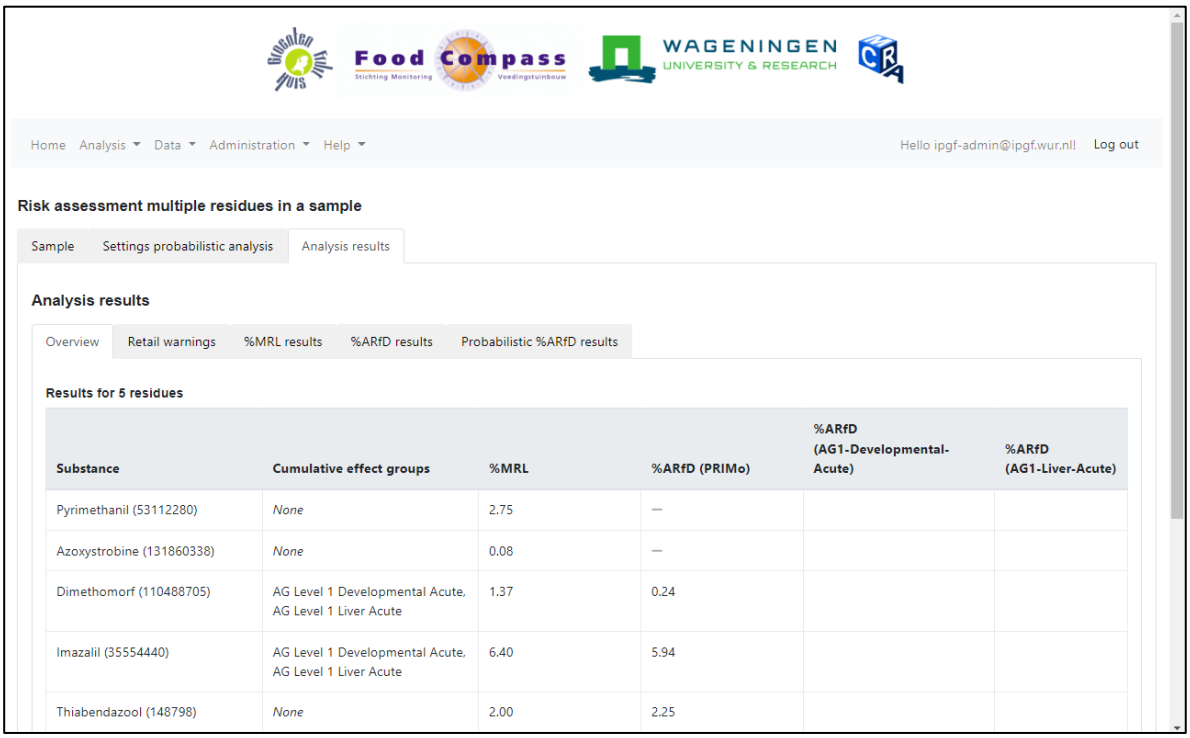

Figure 3 Screenshot of the single sample analysis page showing the results of the deterministic calculations.

4.1.2 Batch analysis

In the portal, a batch of samples can be defined by the user by specifying name, a startdate and an enddate. In the batch analysis, all FoodCompass samples that were sampled during the period defined by the batch are collected in the batch for joint analysis. In the batch analysis, for the legal and above legal deterministic per-sample analysis are performed in the same way as in the single-sample analysis, but now for all samples of the batch. The results are summarized in terms of counts and percentages of samples violating the specific requirements (see Section 3.2 and Section 3.3). For the cumulative risk calculations, the batch of samples is analysed as a whole for each cumulative assessment group available in the database. The results are reported as described in Section 3.1.

Figure 4 shows a screenshot of the batch analyses overview page. On this page, from this page the user can navigate to one of the batch analyses and also create a new batch analysis.

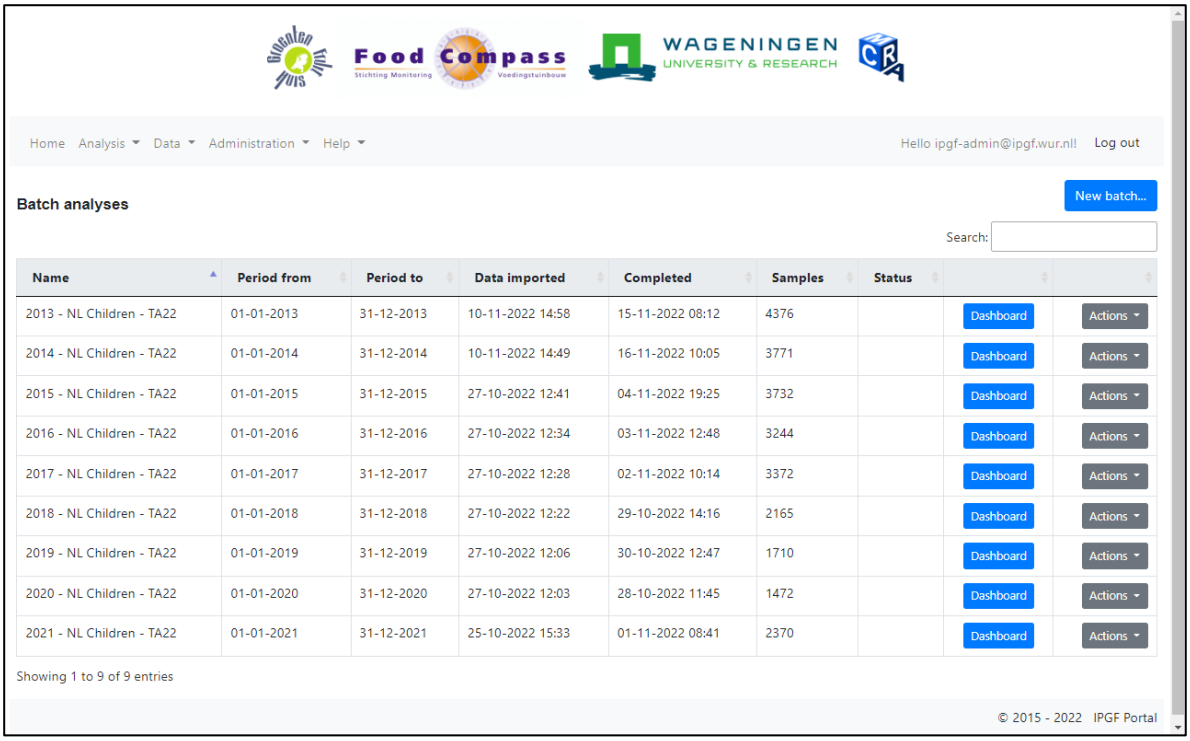

Figure 4 Screenshot of the batch analysis overview page of the IPGF portal.

Figure 5 shows the overview page of a specific batch analysis. The batch analysis page has several sub-pages. Besides the overview page, the user can inspect the samples of the batch, and, after completion of the analysis calculations, is provided several results tabs.

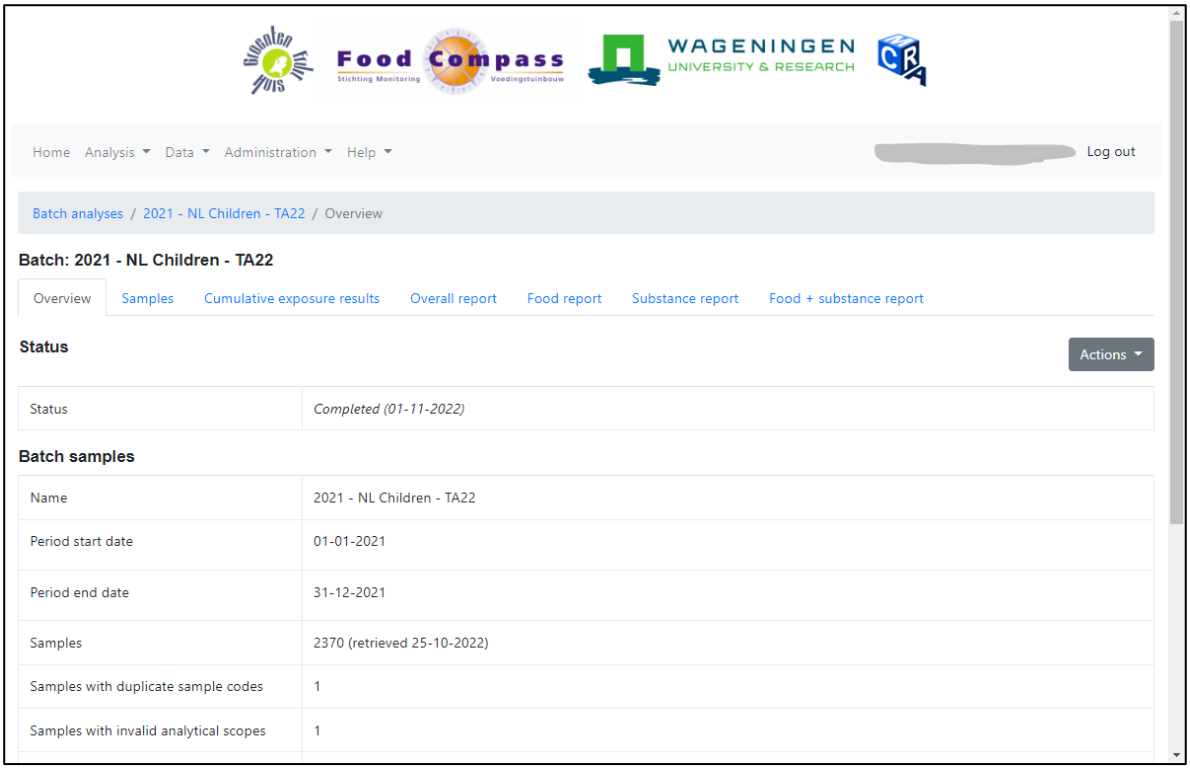

Figure 5 Screenshot the overview page of a batch analysis of the IPGF portal.

4.1.3 Batch comparison analysis

In the batch comparison analysis, the results of multiple batches can simply be combined to evaluate the difference between different batch analyses. In this module, the overall statistics of all batch comparisons are combined in a general overview table, a chart showing the indicator trends, and important risk drivers (i.e., foods, substances, or combinations of food and substance) with high contributions to the computed cumulative risk. Figure 6 shows a screenshot of the cumulative exposures view of the batch comparison page.

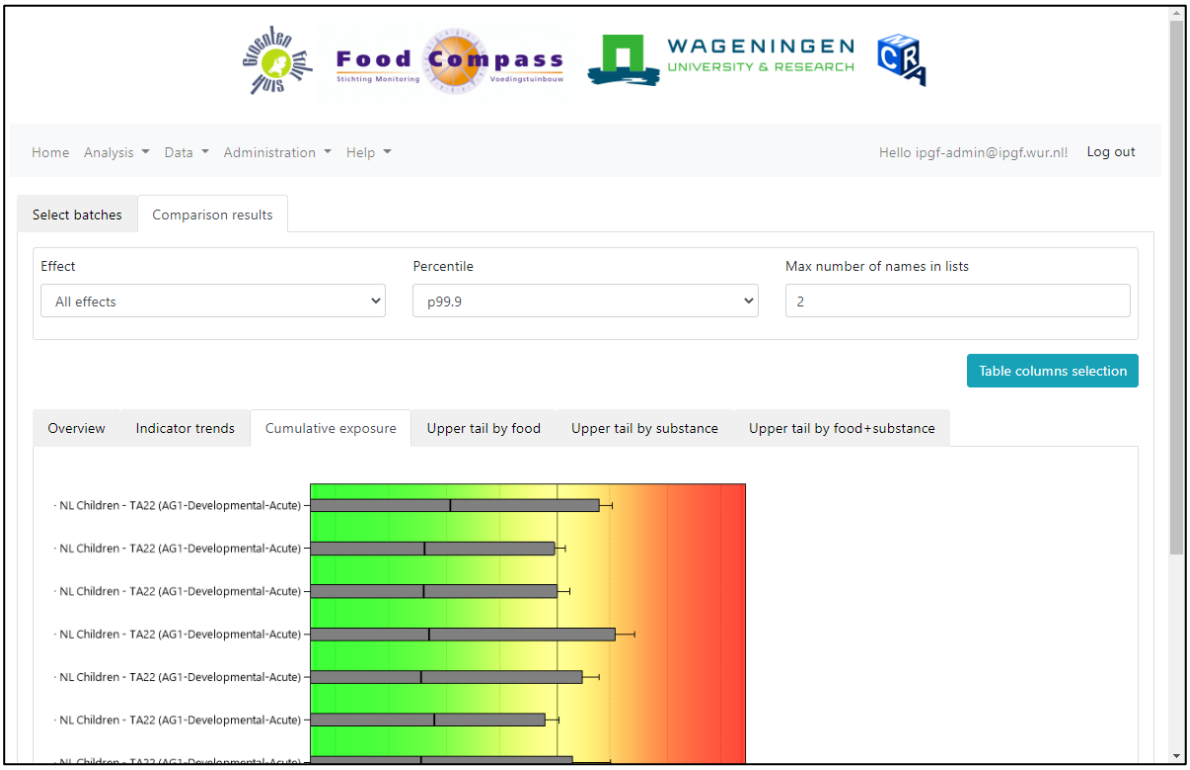

Figure 6 Screenshot of the results view of the batch comparison page. This view shows the chart where the results of the cumulative risk calculations of the effects of highest concern of each batch are combined in one chart.

4.2 Digital infrastructure

All analyses of this case study were performed using the IPGF web portal (version 2.0.0). The IPGF portal is specifically designed to perform impact analyses on the concentrations database maintained by Food Compass. It does so by automatically retrieving the occurrence data from Food Compass via the Food Compass web service, linking it to other data and delegating model calculations to specific modelling services, such as MCRA for cumulative risk calculations and the GroentenFruit Huis web service for IESTI calculations and MRL calculations.

The web service infrastructure of the IPGF portal is depicted in Figure 7. On the left, the two web services of the private sector are depicted, being the Food Compass web service fullfilling a role as a data provider of the monitoring data and the GroentenFruit Huis web service which is used for delegating calculation of the traditional risk indicators. On the right, the MCRA web platform is depicted, offering a service for running cumulative exposure and risk calculations. For this exercise, the IPGF portal is the central hub bringing together data and models from multiple sources.

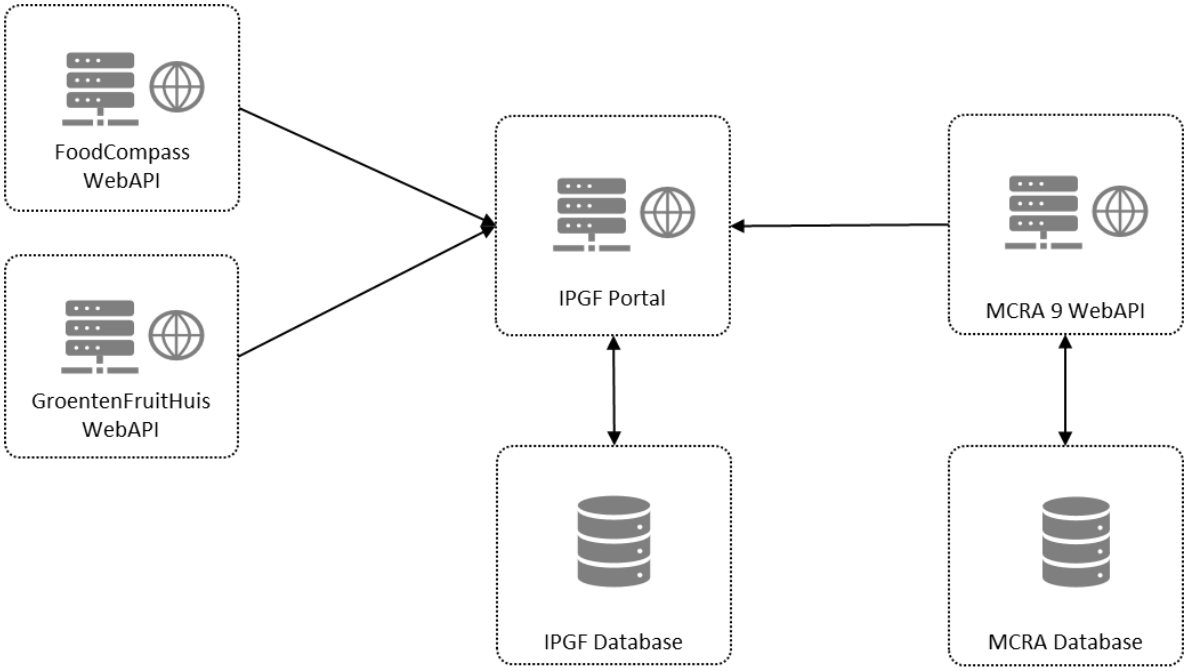

Figure 7 Illustration of the web service infrastructure of the communication and data exchange between the IPGF Portal and other web services.

4.2.1 Food Compass web service

The Food Compass web service is used to retrieve the concentration data and also (part of) the foods catalogue for the analyses. For each batch analysis, the time of retrieval of the monitoring data of the batch is stored considered to be the relevant version timestamp.

4.2.2 GroentenFruit Huis web service

The GroentenFruit Huis web service is used for the IESTI (expressed as percentage of ARfD) and MRL values used for the MRL exceedence calculations. For the analysis of the samples of a batch, the date of the analysis is considered the timestamp for the calculations, which were performed in November 2022.

4.2.3 MCRA web platform

The IPGF portal delegates the cumulative impact analyses to the MCRA platform. The MCRA version used for running the analyses is therefore the version published at the time of running the analysis (version 9.1.49).

5 Results

This section shows the main results of the trend analysis 2013-2021 (Section 5.1), first for the cumulative risk calculations (Section 5.1.3) and then for the deterministic estimates (Section 5.1.1) and private retail requirements (Section 5.1.2), and then provides more detail for the specific year 2021 (Section 5.2) followed by an evaluation of the unquantified uncertainties of the cumuluative risk calculations (Section 5.3).

5.1 Trend analysis monitoring data 2013-2021

5.1.1 Results cumulative risk calculations using MCRA

Figure 8 summarizes the results of the health effect with the highests concern in the cumulative risk assessment, *i.c.* CAG-04 related to adverse effects on the developmental/reproductive system. The selection is based on the upper uncertainty limit of the p99.9 of the HI distribution. In Figure 8, the results of the trend analysis are shown: in each year based on the cumulative risk assessment, the effect with the highest concern is selected and displayed. The safety chart visualizes both variability and uncertainty of the distribution of the total hazard index of the population. The right edges of the grey box indicate the p99.9 percentiles, the median is shown by the vertical line inside the box. The right whisker outside the box indicates the upper p97.5 uncertainty limit of the p99.9 percentile, based on 100 uncertainty runs. The reference line HI = 1 (or exposure equal to 100% of ARfD) is the threshold for possible concern.

In all the years, the CAG with highest concern was CAG-04. Given that this is the largest CAG, with 110 substances, this result might not be too surprising.

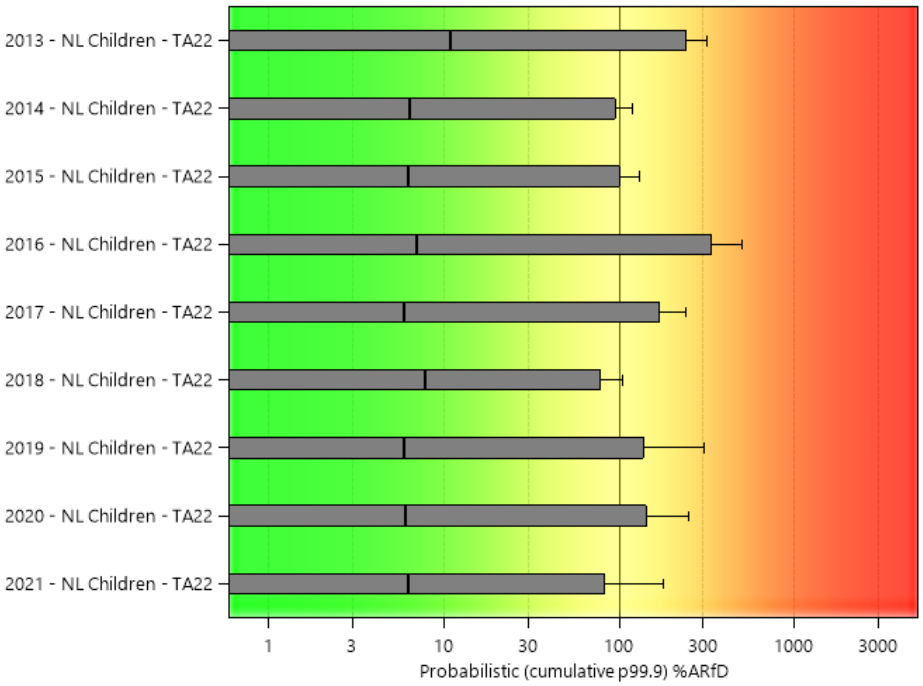

Figure 8 Safety charts of the CAG with the highest concern based on a cumulative exposure assessments for the years 2013-2022. Disclaimer: the risk calculations deviate from EU regulatory accepted methods (see Section 3.1).

Table 7 shows more details on the cumulative assessments. It shows for each year the CAG with the highest potential concern (coincidentally being CAG-04 for all years). For this CAG, the table reports the number of active substances with a positive exposure,

the confidence intervals of the hazard index expressed as a percentage, the probability of exceeding the threshold for possible concern and the combinations of food and substance with the highest contributions to the upper 0.1% of the exposure and risk distribution. Figure 17, Figure 18, and Figure 19 visualise for each year respectively the contributions of the foods, active substances and combinations of foods and substance to the upper 0.1% of the exposure and risk distributions. From the table and the figures it can be seen that the specific risk driving combinations of food and substance change over the years, but that there are recurring foods, substances, and combinations. The food products oranges and mandarins recur in multiple years as do the substances dimethoate and phosmet. Both dimethoate and phosmet are no longer authorised in the EU. Approval of dimethoate expired in 2019 and approval of phosmet expired in 2022.

Table 7. Results cumulative risk assessment for Dutch children, 2013-2021.

Year	Assessment group(s) with potential risk[1]	Number of active substances / with exposure	P99.9 of 100*HI (exposure, as % of ARfD) [95% conf. int.]	Probability of exceeding the threshold for possible concern [95% conf. int.]	Highest contributing combinations of food and substance to the upper p99.9 of the exposure distribution
2013	CAG-04	53	(105, 317)	(0.12, 0.91)	Zoete kersen / Dimethoaat (44%) Spinazie / Indoxacarb (19%) Appelen / Fosmet (9.7%) Tafeldruiven / Methiocarb (7%) Sinaasappelen / Dimethoaat (5.7%)
2014	CAG-04	55	(76.6, 120)	(0.04, 0.16)	Sinaasappelen / Dimethoaat (19%) Spinazie / Cypermethrin (17%) Blauwe bessen / Fosmet (16%) Spinazie / Indoxacarb (10%) Appelen / Fosmet (7.7%) Sinaasappelen / Cypermethrin (7.2%)
2015	CAG-04	55	(71, 131)	(0.04, 0.18)	Blauwe bessen / Fosmet (40%) Spinazie / Cypermethrin (24%) Sinaasappelen / Cypermethrin (4.2%) Spinazie / Indoxacarb (4.1%) Zoete kersen / Dimethoaat (3.5%) Tafeldruiven / Ethephon (2.9%)
2016	CAG-04	57	(147, 505)	(0.21, 0.84)	Haricot vert / Dimethoaat (21%) Chili pepers / Dimethoaat (16%) Spitskool / Dimethoaat (15%) Haricot vert / Cypermethrin (15%) Sinaasappelen / Dimethoaat (14%) Aalbessen (rood) / Fosmet (8.9%)
2017	CAG-04	54	(74, 241)	(0.03, 0.75)	Zoete kersen / Dimethoaat (56%) Appelen / Fosmet (11%) Mandarijnen / Cypermethrin (4.6%) Appelen / Cypermethrin (4%) Sinaasappelen / Cypermethrin (3.3%) Zoete kersen / Tebuconazool (2.1%)
2018	CAG-04	54	(57, 104)	(0.01, 0.11)	Mandarijnen / Propiconazool (58%) Sinaasappelen / Cypermethrin (5.9%) Sinaasappelen / Lambda-Cyhalothrin (5.6%) Appelen / Indoxacarb (2.4%) Sinaasappelen / Propiconazool (2.1%) Tafeldruiven / Indoxacarb (2%)
2019	CAG-04	54	(68, 305)	(0.02, 0.52)	Sinaasappelen / Dimethoaat (61%) Haricot vert / Dimethoaat (14%) Sinaasappelen / Lambda-Cyhalothrin (9.6%)

					Sinaasappelen / Cypermethrin (6.5%) Sinaasappelen / Carbendazim (1.1%) Mandarijnen / Cypermethrin (0.91%)
2020	CAG-04	56	(58, 246)	(0.01, 0.60)	Sinaasappelen / Fosmet (47%) Sinaasappelen / Cypermethrin (20%) Andijvie / Indoxacarb (11%) Spinazie / Indoxacarb (3.6%) Mandarijnen / Lambda-Cyhalothrin (2.4%) Boerenkool / Deltamethrin (2.4%)
2021	CAG-04	51	(53, 179)	(0.00, 0.26)	Peren / Fosmet (39%) Appelen / Captan (19%) Sinaasappelen / Cypermethrin (19%) Appelen / Tebuconazool (3.8%) Ananassen / Ethephon (3%) Peren / Indoxacarb (2.5%)

[1] Listed if uncertainty 97.5 % upper limit of cumulative exposure P99.9 is higher than ARfD.
[2] Median estimate, uncertainty not shown

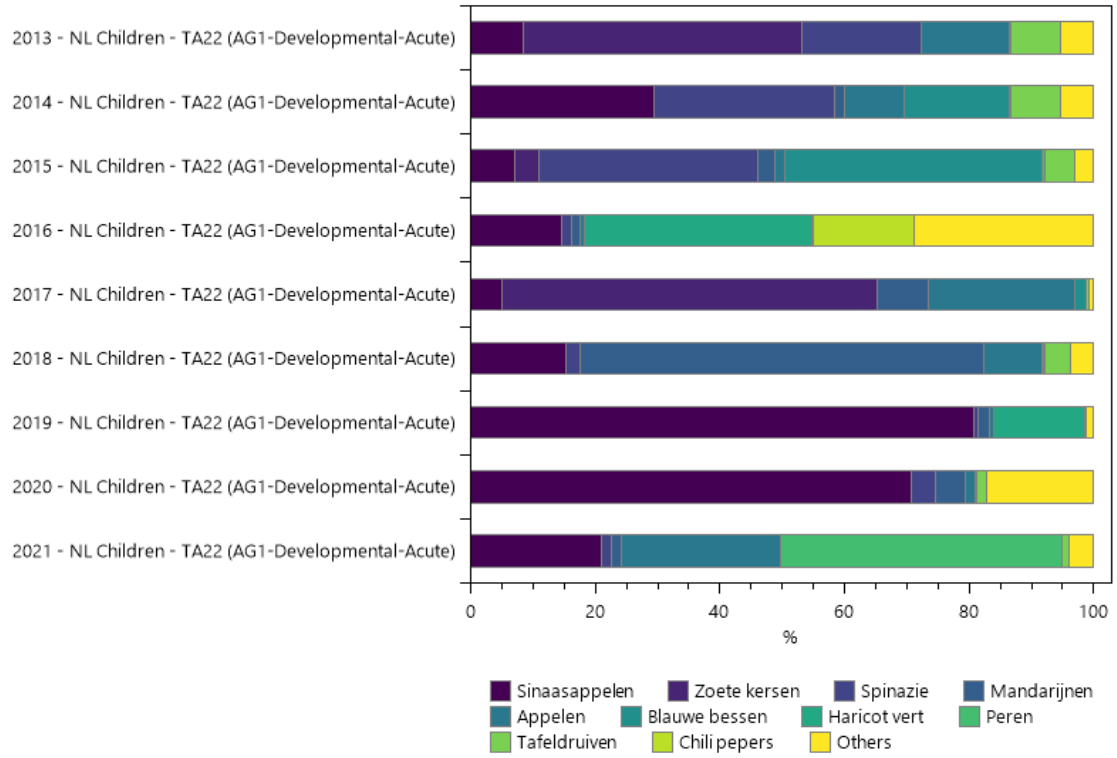

Figure 9 Contributions of foods to the upper tail (0.1%) of the exposure distribution.

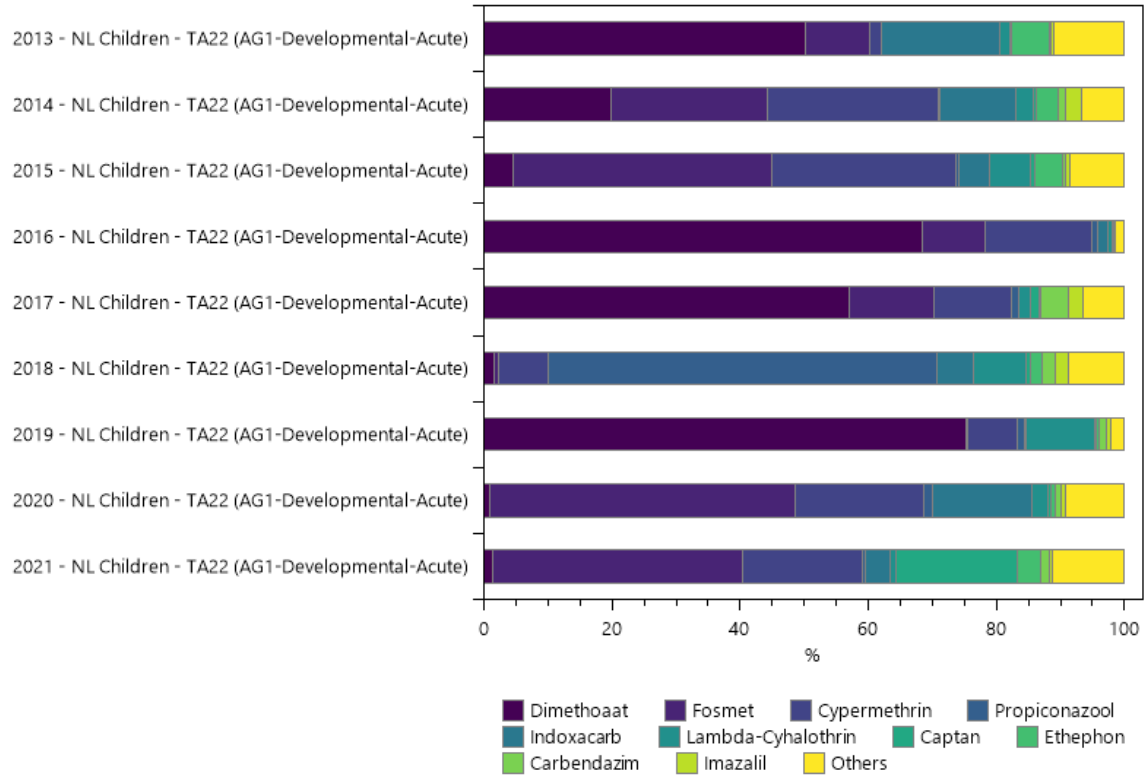

Figure 10 Contributions of substances to the upper tail (0.1%) of the exposure distribution.

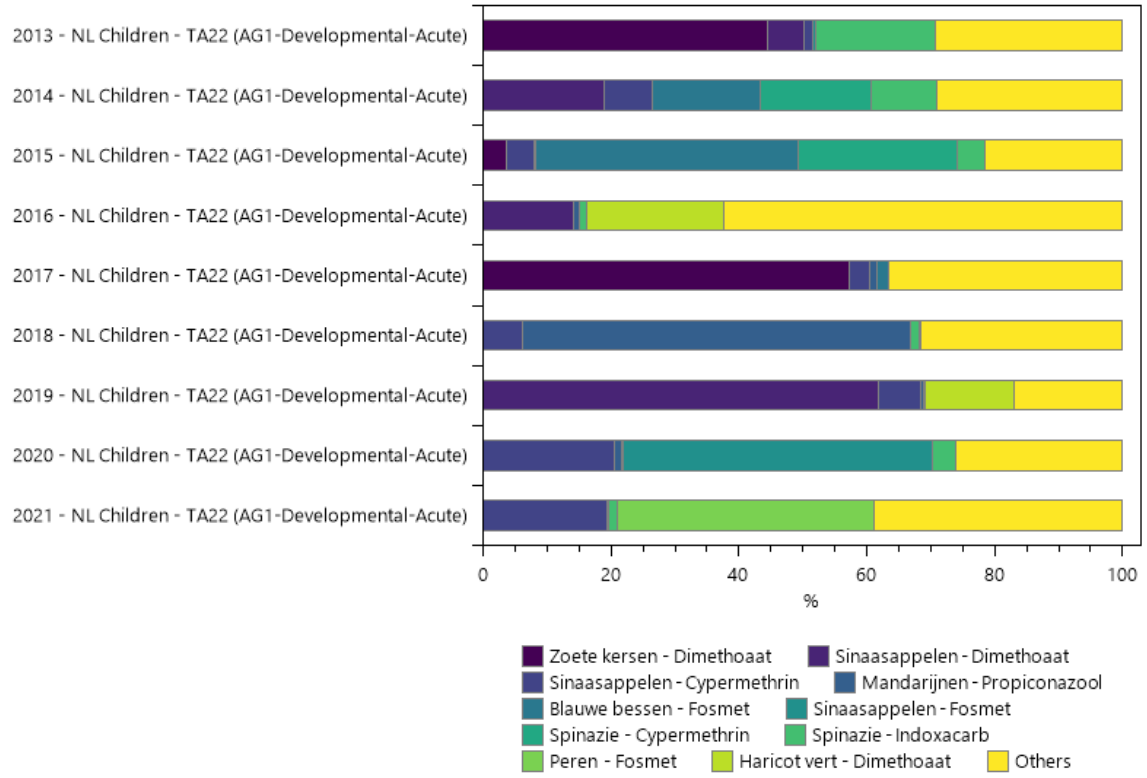

Figure 11 Contributions of foods/substances to the upper tail (0.1%) of the exposure distribution.

5.1.2 Results deterministic sample analyses based on legal requirements

Table 8 shows a summary of findings of residues of CMR and/or substances of which the genotoxic potential cannot be ruled out. The results show a decreasing number of residue findings of residues of both classes of substances. Such a trend can be expected when considering, for instance, chlorpyrifos which was approved until 2020 in the EU (i.e., during the time frame of the trend analysis) because its genotoxic potential could not be ruled out.

Table 8 Summary of the residue findings of CMR substances and substances of which the genotoxic potential could not be ruled out of the batches per year expressed as both as counts and percentages of the total number of samples.

Year	Number of samples in batch	Nr of samples with residues of CMR substances	% of samples with residues of CMR substances	Nr of samples with residues of substances of which genotoxic potential could not be ruled out	% of samples with residues of substances of which genotoxic potential could not be ruled out
2013	4376	42	1.0	179	4.1
2014	3771	43	1.1	194	5.1
2015	3732	50	1.3	202	6.1
2016	3244	50	1.5	228	6.2
2017	3372	46	1.4	185	5.5
2018	2165	32	1.5	153	7.1
2019	1710	28	1.6	72	4.2
2020	1472	24	1.6	35	2.4
2021	2370	18	0.8	6	0.3

Table 9 shows a summary of the MRL exceedance calculations over the years of the trend analysis. It shows the percentage of samples in which an MRL exceedance was detected and also the counts and percentages of the foods, substances, and combinations of food and substances for which any MRL exceedance was observed. The percentage of samples with an MRL exceedance varies between 1 and 3%. In each year, MRL exceedances were observed varying between 29-34%, 22-31% and 5.2-7.3% for analysed foods, substances and food/substance combinations, respectively.

Table 9 Summary of the MRL exceedances of the batches per year.

Year	Number of samples	% of samples with concentration >MRL for any substance	Number of foods with at least one MRL exceedance*	Number of substances with at least one MRL exceedance*	Number of food/ substances combinations with at least one MRL exceedance*
2013	4376	1.6	33 (28.9%)	59 (25.2%)	99 (6.1%)
2014	3771	2.9	32 (29.5%)	64 (27.6%)	139 (9.2%)
2015	3732	1.3	31 (29.5%)	56 (24.1%)	78 (5.2%)
2016	3244	2.9	33 (31.7%)	71 (30.6%)	145 (9.1%)
2017	3372	2.2	34 (34.3%)	55 (25.0%)	92 (6.0%)
2018	2165	2.6	32 (34.4%)	58 (25.9%)	77 (5.8%)
2019	1710	3.2	33 (33.3%)	54 (27.3%)	84 (7.3%)
2020	1472	3.0	29 (30.5%)	45 (21.8%)	65 (6.0%)
2021	2370	2.3	31 (32.5%)	47 (24.1%)	79 (6.4%)

*The number and, within parenthesis, the percentage of foods, substances or food/substance combination exceeding the MRL.

Table 10 summarizes the results of the calculations comparing the IESTI with the ARfD. For all criteria, the percentage of samples with IESTI > ARfD is decreasing.

Table 10 Summary of the sample analyses of the batches per year: IESTI exceeding ARfD.

Year	Number of samples	% of samples with IESTI > ARfD for any substance	Number of foods with at least one ARfD exceedance*	Number of substances with at least one ARfD exceedance*	Number of food/substances combinations with at least one ARfD exceedance*	% of samples with concentration > MRL and IESTI > ARfD for any substance
2013	4376	2.1	22 (19.3%)	19 (8.1%)	115 (7.1%)	0.3
2014	3771	1.9	18 (17.8%)	29 (12.5%)	90 (5.9%)	0.3
2015	3732	1.6	18 (17.1%)	19 (8.2%)	78 (5.2%)	0.3
2016	3244	1.3	19 (18.3%)	22 (9.5%)	66 (4.1%)	0.2
2017	3372	0.8	16 (16.2%)	16 (7.3%)	37 (2.4%)	0.2
2018	2165	0.7	9 (9.7%)	14 (6.2%)	25 (1.9%)	0.3
2019	1710	0.5	7 (7.1%)	10 (5.1%)	12 (1.0%)	0.4
2020	1472	0.6	8 (8.4%)	12 (5.8%)	17 (1.6%)	0.4
2021	2370	0.8	6 (6.2%)	12 (6.2%)	30 (2.4%)	0.1

*The number and, within parenthesis, the percentage of foods, substances or food/substance combination exceeding the ARfD

Figure 12 shows the trend lines for the percentages of MRL exceedance, ARfD exceedances, the combination of MRL and ARfD exceedance, residue findings of CMR substances and substances of which genotoxic potential could not be ruled out. Except for the percentage of samples with residue findings of substances of which genotoxic potential could not be ruled out and the percentages of samples in which the IESTI exceeds the ARfD, all indicators remain stable over the years of the analysis.

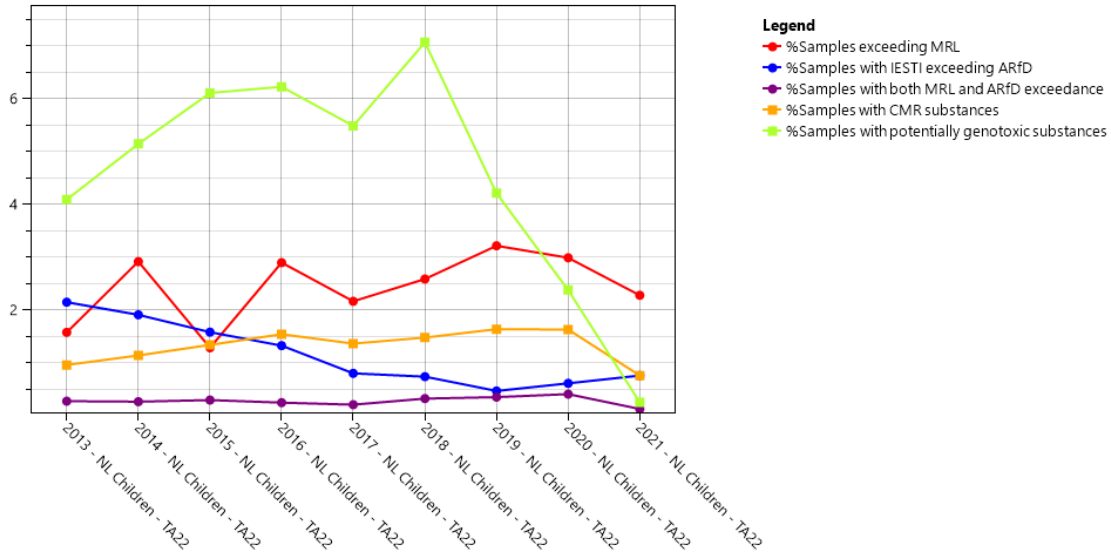

Figure 12 Trendlines of the percentages of samples not matching with legal indicators.

5.1.3 Results of testing for compliance with retail restrictions

Table 11 and Figure 13 summarize and visualize the results of the evaluation of compliance with retail restrictions.

Percentages for the maximum number of substances shown in Table 11 vary between 2 and 18%. In this criterion all active substances are considered instead of all substances recorded in the blacklists, adopted by some retailers. As a consequence,

these percentages will be lower in the latter case. The summary also shows that percentages of samples that fail to comply with the MRL criteria are higher than the percentages for the ARfD. For the MRL criteria, also note that more samples fail to comply with the criterion 'any substance residue exceeding the %MRL defined threshold' than compared to the criterion 'exceeding the sum of the %MRL used of the substance residues'. This is explained by the lower threshold used for the criterion on single %MRL compared to the threshold used for the criterion on the sum of MRL percentages (for Retailer I, 33 and 80% respectively). No clear trends are visible over the time frame of the trend analysis.

Table 11 Retail criteria assessment

Year	% of samples exceeding any retail criterion on max. number of substances	% of samples exceeding any retail criterion on single %MRL	% of samples exceeding any retail criterion on sum %MRL	% of samples exceeding any retail criterion on single %ARfD	% of samples exceeding any retail criterion on sum %ARfD	% of samples exceeding any retail criterion
2013	19.3	10.1	6.2	4.5	3.8	25.6
2014	22.5	11.7	7.4	4.2	4.0	28.9
2015	19.1	11.3	6.9	4.4	4.1	25.3
2016	20.1	14.6	9.1	3.8	3.2	28.1
2017	19.6	11.7	7.7	2.4	2.7	25.6
2018	22.8	13.9	9.5	3.8	3.8	28.9
2019	19.2	13.5	8.4	2.6	2.9	26.8
2020	18.5	12.3	8.3	2.9	3.5	25.3
2021	22.3	11.4	8.5	3.1	4.5	28.0

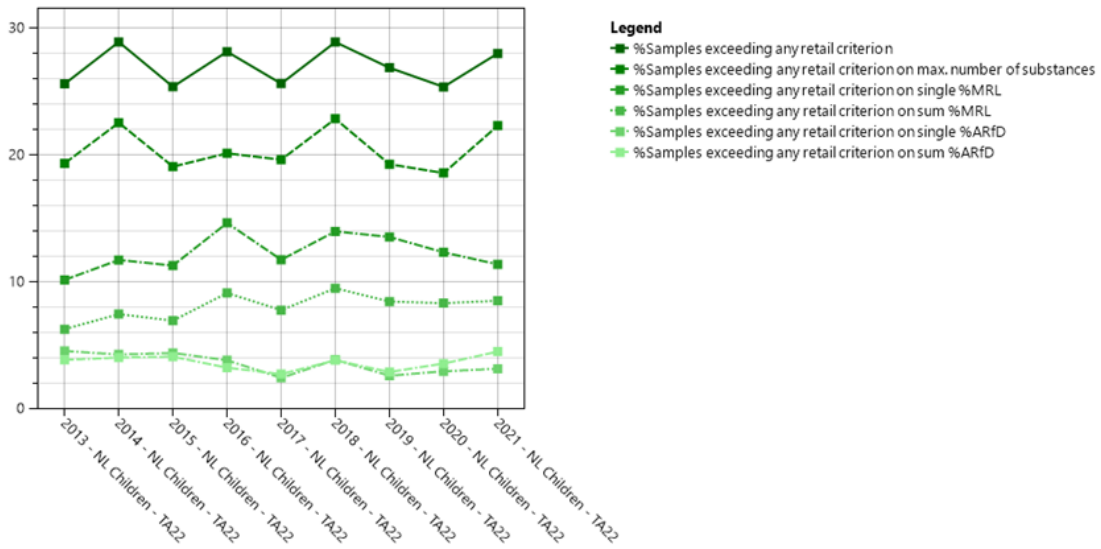

Figure 13 Trendline of the percentage of samples not complying with the retail requirements. The top line shows the percentage of exceedance of any retail criterion and the other lines show the percentages per rule.

5.2 Results cumulative assessment 2021

Table 12 summarizes the results of the cumulative risk calculations of the batch of samples collected in 2021. It shows for each CAG, the cumulative exposure, the median, lower and upper uncertainty limit of the HI at the p99.9 percentile of the

exposure distribution, and the median, lower and upper uncertainty limit of the probability of exceeding the threshold for possible concern (POCE). It shows that CAG-04 has the highest estimated exposure and risk, having a median HI% just below 100%, but an upper p97.5 uncertainty limit exceeding 100%. In total, in three of the 15 CAGs, the upper P97.5 uncertainy limit exceeds the 100% threshold.

Table 12 Results of the cumulative risk calculations of the samples of the year 2021.

CAG	Cum. exposure (µg/kg/day)	P99.9 of 100*HI (exposure, as % of ARfD) (median)	P99.9 of 100*HI (exposure, as % of ARfD) (p2.5)	P99.9 of 100*HI (exposure, as % of ARfD) (p97.5)	POCE %	POCE % (p2.5)	POCE % (p97.5)
CAG-04	0.0998	99.8	71	131	0.101	0.0384	0.18
CAG-10	0.0959	95.9	65.1	128	0.091	0.035	0.163
CAG-08	0.0889	88.9	63.6	116	0.0725	0.0244	0.133
CAG-05	0.0607	60.7	38.5	84.7	0.039	0.005	0.0821
CAG-07	0.314	31.4	22.1	42.3	0.002	0	0.0106
CAG-06	0.026	26	21.3	32	0	0	0.00252
CAG-13	0.955	19.1	14.1	25.3	0	0	0
CAG-14	0.549	13.7	9.42	19.4	0	0	0
CAG-15	0.636	12.7	7.18	19.1	0	0	0
CAG-09	0.629	12.6	8.79	18.9	0	0	0
CAG-01	0.345	6.89	3.88	11.6	0	0	0
CAG-02	0.561	4.31	1.92	11	0	0	0
CAG-03	0.0772	1.54	0.886	3.19	0	0	0
CAG-12	0.29	0.579	0.333	0.72	0	0	0
CAG-11	0.0112	0.112	0.11	0.155	0	0	0

For 2021, the highest cumulative hazard index in the results of the cumulative impact analysis was found for CAG-04. In the remainder of this section we will zoom in on the results of the cumulative risk calculations of this CAG.

The overall result of the cumulative analysis is visualised by a safety chart, see **Error! R eference source not found.**. Here the upper uncertainty limit of the p99.9 percentile exceeds the threshold (0.26%).

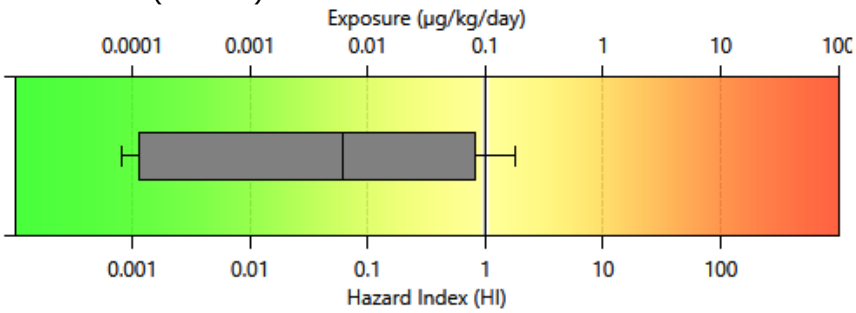

Figure 14 Safety chart of the hazard index showing the lower and upper bound of the variability distribution, p0.1 and p99.9 respectively, and the lower and upper uncertainty bound, p2.5 and p97.5 respectively of the p0.1 and p99.9 variability percentiles. Disclaimer: the risk calculations deviate from EU regulatory accepted methods (see Section 3.1).

Figure 15, left plot, shows the hazard index distribution estimated in the nominal analysis. The boxplots (right) for uncertainty show the p25 and p75 as edges of the box, and p2.5 and p97.5 as edges of the whiskers. The reference value is indicated with the dashed black line, the median with the solid black line within the box. Outliers are displayed as dots outside the whiskers.

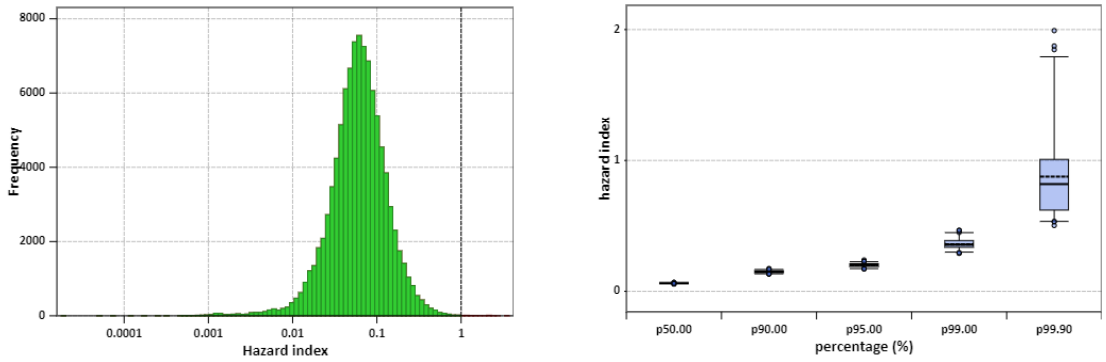

Figure 15 Left: hazard index distribution of 100.000 simulated individual days. Right: boxplots showing the uncertainty limits of the percentiles p50, p90, p95, p99 and p99.9 based on 100 uncertainty runs.

In **Error! Reference source not found.**, the cumulative hazard index is based on 110 s ubstances, although 58 substances had no positive intake via the investigated food products or drinking water, and therefore did not contribute. Figure 16 displays the cumulative or total HI together with the per-substance hazard quotients (here also named HIs) for the top 10 and bottom 3 substances with exposure. Fosmet is the most important contributor to the cumulative HI with upper uncertainty limit exceeding the threshold for possible concern.

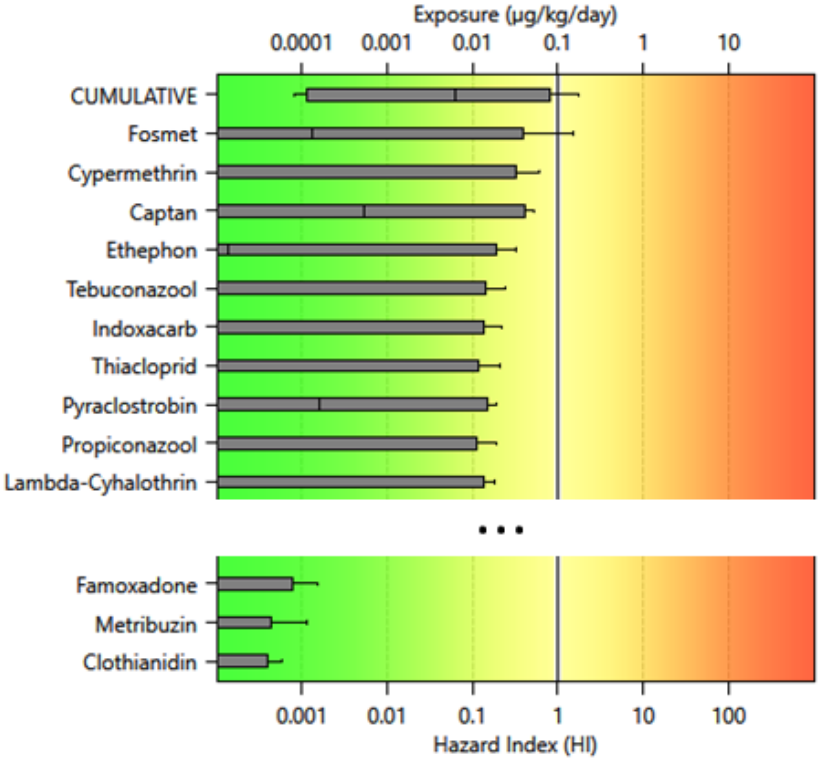

Figure 16 Hazard index (quotients) by substances for the results of the cumulative risk calculations for the CAG for the development system. A selection of the top 10 and bottom 3 substances is shown (out of 51 active substances with positive exposure in total). Disclaimer: the risk calculations deviate from EU regulatory accepted methods (see Section 3.1).

Figure 17 shows a pie chart of the contributions of the individual foods to the upper 0.1% of the population according to the exposure distribution. The upper part of the distribution is of interest because it contains the individuals with high exposure. When possible concern is identified for the p99.9 percentile, this pie chart shows the food products that are in particular responsible for the high exposures. Here, pears (43.8%), apples (24.8%) and oranges (20.3%) are the main contributors to the exposure.

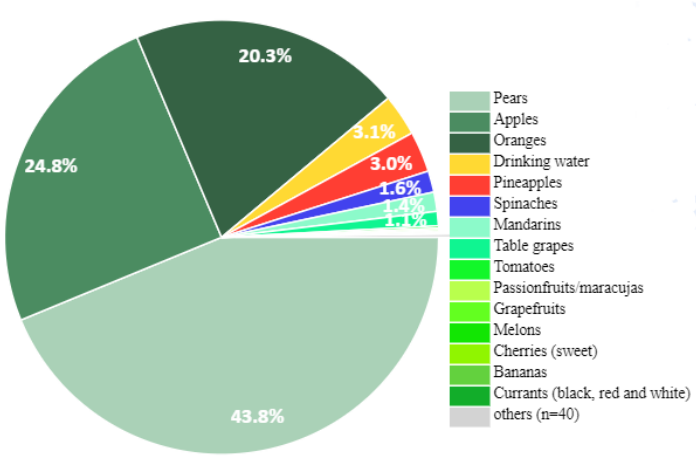

Figure 17: Contributions of raw (modelled) foods to the upper 0.1% of the cumulative exposure distribution.

An analysis of the upper tail of the exposure distribution for foods as eaten shows in Figure 18, that pears with unspecified processing (36.2%), apples (juiced) (23.7%) and oranges (juiced) (19.7%) contribute the most.

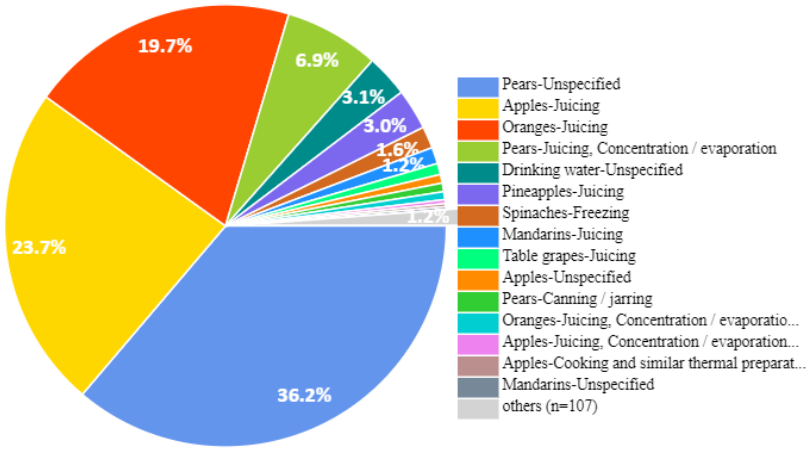

Figure 18: Contributions of processed foods to the upper 0.1% of the cumulative exposure distribution.

In Figure 19, the substances contributing to the upper tail (0.1%) of the exposure distribution are shown. Phosmet has the highest contribution, 39%. In the total exposure distribution Captan (23.3%) followed by Ethoprofos (18.1%) are the most important substances (results not shown).

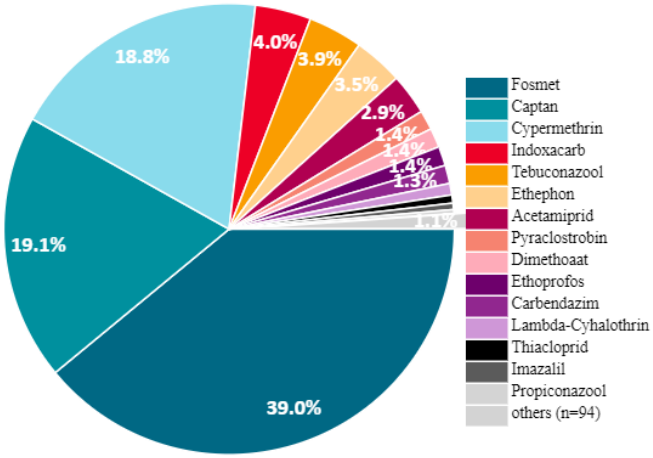

Figure 19: Contributions of substances to the upper 0.1% of the cumulative exposure distribution.

Error! Reference source not found. and Table 13 show the top contributing combinations of food, substance and processing type to the upper p99.9 of the exposures. In **Error! Reference source not found.**, a summary is given for the mean c ontribution of each combination of processed food and substance computed over all uncertainty runs. Table 13 shows also the lower and upper p2.5 and p97.5 confidence bounds of the contributions, as well as the processing factor that was available for this combination. Here it can be seen that the combination of phosmet on pears with unspecified processing has the highest contribution (32.2%) followed by cypermethrin on oranges with processing type juicing (18.2%) and captan on apples with processing juicing (18.1%). The table also shows that for none of the combinations in the table a processing factor was available. It can also be observed that drinking water is only just amongst the top contributing combinations. This is due to the fact that for drinking water a relatively conservative imputation method is adopted, by assigning fixed high concentration values for the five most toxic substances.

Table 13: Exposure statistics by modelled food, substance and processing types (upper distribution).

Substance name	Food name	Processing type	Contribution (%) mean	Contribution (%) lower bound (p2.5)	Contribution (%) upper bound (p97.5)	Processing factor	Processing correction factor
Fosmet	Pears	Unspecified	32.2	0.0	76.7	1	1
Cypermethrin	Oranges	Juicing	18.2	0.0	72.5	1	1
Captan	Apples	Juicing	18.1	0.3	58.8	1	1
Fosmet	Pears	Juicing, Concentration / evaporation	6.1	0.0	16.8	1	1
Tebuconazool	Apples	Juicing	3.7	0.0	20.2	1	1
Ethephon	Pineapples	Juicing	3.0	0.1	19.2	1	1
Indoxacarb	Pears	Unspecified	2.1	0.0	5.0	1	1
Acetamiprid	Pears	Unspecified	1.7	0.0	4.1	1	1
Dimethoaat	Drinking water	Unspecified	1.4	0.7	3.0	1	1
Ethoprofos	Drinking water	Unspecified	1.4	0.7	3.0	1	1

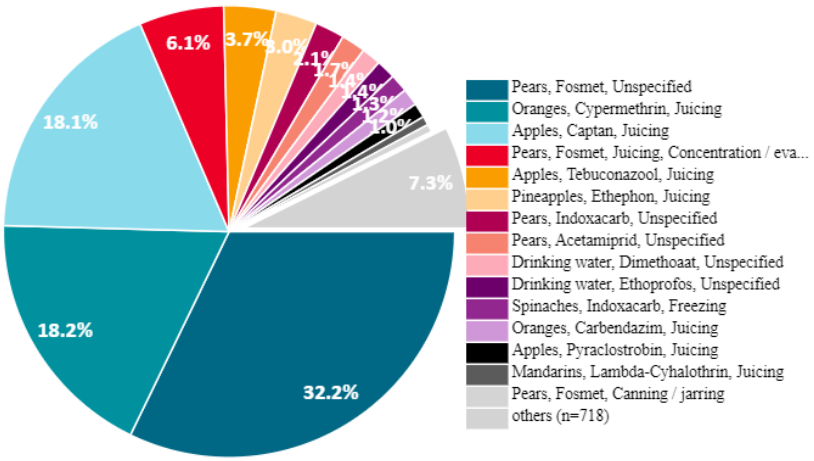

Figure 20: Contributions of processed (modelled) foods and substances to the upper 0.1% of the cumulative exposure distribution.

5.3 Analysis unquantified uncertainties cumulative impact assessments

The cumulative risk assessments include quantified analyses of the sampling uncertainties of the consumption and concentration data. Besides this, there are also a number of uncertainty sources that are not quantified. This section restricts to the analysis of uncertainty sources and the potential bias they cause in the results. These sources highly overlap with the uncertainties identified in (EFSA, 2020a, EFSA, 2020b, EFSA, 2021). This section will focus mainly on the aspects particular for the present cumulative assessments.

5.3.1 Uncertainties in consumption data

The uncertainties in the consumption data addressed in (EFSA, 2020a, EFSA, 2020b, EFSA, 2021) also apply for the cumulative assessments in this study. For this study in particular, the consumption dataset of the Dutch children, calculated for raw primary commodities, has no consumptions for a number of foods. Not including these products, can be regarded as an optimistic assumption and the computed risk could be lower than the actual risk.

There are two probable causes for this uncertainty: some food products were not consumed by any of the survey participants and/or a linking problem or coding conversion problem exist. Considering the first cause for foods that are not frequently consumed, the impact on the cumulative exposure and risk is low, unless very high concentrations have been measured. For the foods that were missing due to linking mismatches, the cumulative exposure or risk is underestimated. Table 14 summarizes the measured foods for which no consumptions were found in the consumption data. For these foods, it is also manually checked whether consumptions were available in the original data collection, meaning the foods were not consumed or whether the foods were not found due to a linking problem. The table shows that there are a number of food products for which a linking problem occurred.

Table 14 Measured food products for which no consumptions were found in the consumption data.

Modelled food name	Modelled food code	In original consumption data
Limes	P0110040A	No
Quinces	P0130030A	No
Kaki/Japanese persimmons	P0161060A	Yes
Papayas	P0163040A	No
Granate apples/pomegranates	P0163050A	Yes
Sweet potatoes	P0212020A	No
Shallots	P0220030A	No
Okra (lady's fingers)	P0231040A	No
Roman rocket/rucola	P0251060A	No
Purslanes	P0252020A	No
Chards/beet leaves	P0252030A	No
Tarragon	P0256100A	No
Peas (with pods)	P0260030A	Yes

Rhubarbs	P0270070A	Yes
Other cucurbits with edible peel	P0232990A	No
Witloofs/Belgian endives	P0255000A	No
Other cucurbits with inedible peel	P0233990A	No
Turnips	P0213110A	No
Parsnips	P0213060A	No
Baby leaf crops (including Brassica species)	P0251080A	No
Red mustard	P0251070A	No
Cherimoya	P0163060A	No

5.3.2 Uncertainties in concentration data

Besides the sampling uncertainty of the concentration data, it should also be noted that not every food item is equally well represented in the data. In some years, some foods have not been sampled. Also for specific combinations of foods and substances data may be lacking. This leads to an underestimation of the actual exposure and risk.

In addition, for each year there were several samples with invalid measurements. These invalid measurements were reported positive concentration measurements of substances that were not known to be part of the reported analytical method. These invalid measurements were not included in the cumulative exposure assessments.

For allocation of active substances and imputation of missing and and left-censored concentration measurements (non-detects), the EU accepted methodology uses information on authorisation of substances on food products to determine whether missing values should be replaced by positive concentration values or regarded as zero/not present in the sample. The motivation for making the distinction between authorised and unauthorised uses is that for unauthorised substance uses it is more likely that missing values and non-detect measurements are zero. By not including this informations the calculations of the presented case study can be assumed more conservative on this aspect than the EU regulatory accepted methodology.

5.3.3 Uncertainty of processing and missing processing factors

Processing factors are included in the model to account for the assumption that processing often reduces the actual pesticide residue levels on the food products. Getting information on processing factors for all combinations of food items, processing types and substances is cumbersome or even impossible. Processing factors are therefore only available for a limited number of combinations of food, active substance and processing type for which reliable data were available. The default assumption is that processing does not affect the residue levels and no processing factor is applied, which is a conservative estimate.

Also the processing factors included in the calculations are subject to uncertainty which is not included in the calculations. The effect hereof is that the reported uncertainty bounds are too narrow.

5.3.4 Uncertainty of unit variability factors

Unit variability factors for only 30 products were included. For all other products, unit-to-unit variability was ignored. Including unit variability in the cumulative exposure calculations increases variability and as a consequence leads to a wider exposure and risk distribution. Then, especially at high percentiles, the estimated exposure or risks can be much higher. Ignoring this source of uncertainty is therefore an optimistic assumption.

5.3.5 Uncertainty of the effects and substance grouping

By using the provisional CAGs of Nielsen et al. (2012), the memberships of active substances for each CAG are highly uncertain. It should be noted that Nielsen et al. were interested in chronic risks, whereas in this report acute risks are studied.

Grouping of substances based on a common effect at organ level is a very conservative approach, leading to an overestimation of the actual risks. Substances that have adverse health effects on the same organs may still have different unrelated effects that follow different pathways and lead to unrelated adverse outcomes. This particularly applies to the CAG for the developmental/reproductive system, which is the largest CAG of the case study and observed to be the CAG with the highest calculated hazard indexes of all cumulative assessments in all years. This CAG is actually a combined CAG for two different systems (the developmental and reproductive system), but also within these two systems a multitude of different unrelated phenomenological effects can be distinguished. As mentioned in Section 2.4, the EFSA strategy is to perform potentially multiple cumulative assessments per organ, namely for each identified specific phenomenological effect of the organ. This leads to smaller CAGs, but the number of cumulative assessment groups to be evaluated increases.

5.3.6 Uncertainty of the hazard characterisations

In the calculations, substance hazards are characterised by means of ARfDs (effective in 2022) and reference values defined for the critical effect. That is, based on the lowest dose for which any effect was observed. However, for substances that are associated with multiple effects, this dose only applies for the most critical effect. For other effects, the reference dose will be equal or higher (i.e., less toxic). Using ARfDs is therefore a very conservative approach, leading to an overestimation of the exposure and risks. In addition, ARfDs include a conservative uncertainty factor/safety factor (commonly set to 100) to translate the reference dose obtained from animal studies to a reference dose for humans.

6 Discussion and conclusions

The IPGF web portal successfully demonstrates how the MCRA platform can be accessed via web services and used for specific purposes by other software tools. The IPGF portal brings together the data collected by the private sector with the models for cumulative exposure and risk calculation provided by the MCRA software and allows the user to perform specific modelling tasks tailored for use by the sector as part of its food safety monitoring program.

For the private sector, the cumulative impact analyses made available by the IPGF portal provides a different view on the potential impact of pesticide residues on fruits and vegetables than the traditional per-active-substance indicators by analysing all samples of a year as a whole set. This provides insight in the cumulative impact of all products and all substances together. Also, it allows for identification of risk-driving combinations of substances and foods from the perspective of this overall assessment. This could identify different risk-driving foods and substances than when considering each active substance and food sample individually.

In this report, a case study was used to illustrate the potential of the IPGF portal for embedding cumulative impact assessment in the monitoring program of Food Compass. More specifically, an analysis over the years 2013-2021 of the monitoring data of pesticide residues on fruit and vegetables of Food Compass was carried out. For each year, risk indicators from cumulative impact analyses, indicators based on legal requirements, and indicators of fullfilling the the above legal private retail requirements were computed using the IPGF portal. The results of the case study demonstrate that the IPGF portal allows the sector to efficiently perform cumulative risk calculations on its own monitoring data.

As an example of results obtained with IPGF and MCRA, it is interesting to note that the substances dimethoate and phosmet have a high contribution to the cumulative risk in many of the years of the trend analysis, which are substances that are no longer authorised. For dimethoate, the ARfD has been decreased in 2018 from 0.01 mg/kg bw per day to a suggested acute reference dose of 0.0001 mg/kg bw per day (EFSA, 2018b). Similarly, for phosmet the acute reference value of 0.001 mg/kg bw per day was used, where this was 0.045 mg/kg bw per day previously. In the retrospective cumulative exposure calculations, such unauthorised substances that were authorised at the time of sampling can be expected to stand out in the earlier years, but their contributions should decrease in the years that these substances are not authorised anymore. Similar results were also observed in the previous trend analysis over 2013-2020 (van der Voet et al. 2022) in which chlorpyrifos was identified as a risk driver, also due to the use of an artificially set high reference dose. When considering the cumulative analysis of the year 2021, dimethoate is no longer part of the risk driving substances. It can be expected that phosmet, for which the authorisation expired in the EU more recently (May 1, 2022), would disappear from the results of a future cumulative assessment of the data of 2022.

For demonstrating the IPGF portal a number of pragmatic choices were made regarding the methods and data for the cumulative risk calculations of the case study. In risk assessments of EFSA, CAGs based on common specific phenomenological effects (level 2) are used. However, these are only available for a limited number of effects (EFSA 2020a, EFSA 2020b, EFSA 2021). Further work on defining level 2 CAGs and applying these in cumulative exposure and risk assessments is ongoing at the European level. By using a large collection of provisional CAGs grouped at organ level (level 1, derived from the work of Nielsen et al. (2012)) the IPGF tool has shown to be ready for an anticipated future in which more and more CAGs become available. The use of CAGs at level 1 required a different method for obtaining hazard characterisations which were derived (mostly) from ARfDs, and refinement of the data

with additional processing factors for risk-driving combinations of food, substance, and processing type. The consequence of these choices is that the results of the cumulative risk calculations cannot be regarded as risk assessments compliant with EU regulatory accepted methods. In particular the use of provisional CAGs at level 1 in combination with hazard characterisations derived from generic ARfDs who may or may not be based on the specific target organ makes the calculations very conservative.

The IPGF portal was designed to be flexible for changes in methodology and data. For future implementation, the CAGs and reference values established by EFSA can be linked in instead of the current provisional CAGs. This would be essential for alignment with the risk assessments performed by RIVM and EFSA. Besides this, the calculations of the tool can also be improved by refinement of the data, e.g., by collecting additional processing factors and addressing the other identified unquantified uncertainties (see Section 5.3). Extension with CAGs and methods for assessing chronic (cumulative) exposure and risk would improve the coverage of the risk analyses provided by the toolbox. In this way, iterative refinement of the tool, the methods and the data leads to increasingly more reliable quantification of the cumulative impacts.

For unauthorised substances, and in particular specific classes of substances, such as CMR substances, the methods of the toolbox could be further improved. For the deterministic analyses based on legal requirements, their mere presence should raise warning flags. However, for the cumulative risk calculations, these substances require reference values specific to the health effect that is under consideration. The toolbox could be updated to clearly make this distinction and possibly include reports of unauthorised substances also in the cumulative risk calculations.

Recently, RIVM published a factsheet presenting the results of cumulative risk assessments for the two accepted level 2 CAGs for the nervous system[4]. In these calculations, monitoring data of the Netherlands Food and Consumer Product Safety Authority (NVWA) of the years 2019-2021 was used in combination with consumption data of multiple subgroups of the Dutch population (including the children age 1-6). Differences in the CAGs, hazard characterisations, and the time frame of the monitoring data make these results are not directly comparable with the results for the CAG for the nervous system presented in this report. However, the calculations performed by RIVM can serve as an example for future improvement of the system and alignment with regulatory accepted methods.

[4] https://www.rivm.nl/publicaties/gelijktijdige-blootstelling-aan-verschillende-gewasbeschermingsmiddelen-via-voedsel

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